Cochrane Library

Cochrane Database of Systematic Reviews

Oxycodone for neuropathic pain in adults (Review)

Gaskell H, Derry S, Stannard C, Moore RA

Gaskell H, Derry S, Stannard C, Moore RA.
Oxycodone for neuropathic pain in adults.
Cochrane Database of Systematic Reviews 2016, Issue 7. Art. No.: CD010692.
DOI: 10.1002/14651858.CD010692.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Oxycodone for neuropathic pain in adults

Helen Gaskell[1], Sheena Derry[1], Cathy Stannard[2], R Andrew Moore[1]

[1]Pain Research and Nuffield Department of Clinical Neurosciences (Nuffield Division of Anaesthetics), University of Oxford, Oxford, UK. [2]Pain Clinic, Macmillan Centre, Frenchay Hospital, Bristol, UK

Contact address: Helen Gaskell, Pain Research and Nuffield Department of Clinical Neurosciences (Nuffield Division of Anaesthetics), University of Oxford, Oxford, Oxfordshire, UK. helen.gaskell@ndcn.ox.ac.uk.

Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 7, 2016.

Citation: Gaskell H, Derry S, Stannard C, Moore RA. Oxycodone for neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 2016, Issue 7. Art. No.: CD010692. DOI: 10.1002/14651858.CD010692.pub3.

ABSTRACT

Background

This is an update of an earlier review that considered both neuropathic pain and fibromyalgia (Issue 6, 2014), which has now been split into separate reviews for the two conditions. This review considers neuropathic pain only.

Opioid drugs, including oxycodone, are commonly used to treat neuropathic pain, and are considered effective by some professionals. Most reviews have examined all opioids together. This review sought evidence specifically for oxycodone, at any dose, and by any route of administration. Separate reviews consider other opioids.

Objectives

To assess the analgesic efficacy and adverse events of oxycodone for chronic neuropathic pain in adults.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE from inception to 6 November 2013 for the original review and from January 2013 to 21 December 2015 for this update. We also searched the reference lists of retrieved studies and reviews, and two online clinical trial registries. This update differs from the earlier review in that we have included studies using oxycodone in combination with naloxone, and oxycodone used as add-on treatment to stable, but inadequate, treatment with another class of drug.

Selection criteria

We included randomised, double-blind studies of two weeks' duration or longer, comparing any dose or formulation of oxycodone with placebo or another active treatment in chronic neuropathic pain.

Data collection and analysis

Two review authors independently searched for studies, extracted efficacy and adverse event data, and examined issues of study quality and potential bias. Where pooled analysis was possible, we used dichotomous data to calculate risk ratio and numbers needed to treat for one additional event, using standard methods.

We assessed the evidence using GRADE (Grading of Recommendations Assessment, Development and Evaluation) and created a 'Summary of findings' table.

Main results

The updated searches identified one additional published study, and one clinical trial registry report. We included five studies reporting on 687 participants; 637 had painful diabetic neuropathy and 50 had postherpetic neuralgia. Two studies used a cross-over design and three

used a parallel group design; all studies used a placebo comparator, although one study used an active placebo (benztropine). Modified-release oxycodone (oxycodone MR) was titrated to effect and tolerability. One study used a fixed dose combination of oxycodone MR and naloxone. Two studies added oxycodone therapy to ongoing, stable treatment with either pregabalin or gabapentin. All studies had one or more sources of potential major bias.

No study reported the proportion of participants experiencing 'substantial benefit' (at least 50% pain relief or who were very much improved). Three studies (537 participants) in painful diabetic neuropathy reported outcomes equivalent to 'moderate benefit' (at least 30% pain relief or who were much or very much improved), which was experienced by 44% of participants with oxycodone and 27% with placebo (number needed to treat for one additional beneficial outcome (NNT) 5.7).

All studies reported group mean pain scores at the end of treatment. Three studies reported a greater pain intensity reduction and better patient satisfaction with oxycodone MR alone than with placebo. There was a similar result in the study adding oxycodone MR to stable, ongoing gabapentin, but adding oxycodone MR plus naloxone to stable, ongoing pregabalin did not show any additional effect.

More participants experienced adverse events with oxycodone MR alone (86%) than with placebo (63%); the number needed to treat for an additional harmful outcome (NNH) was 4.3. Serious adverse events (oxycodone 3.4%, placebo 7.0%) and adverse event withdrawals (oxycodone 11%, placebo 6.4%) were not significantly different between groups. Withdrawals due to lack of efficacy were less frequent with oxycodone MR (1.1%) than placebo (11%), with a number needed to treat to prevent one withdrawal of 10. The add-on studies reported similar results.

We downgraded the quality of the evidence to very low for all outcomes, due to limitations in the study methods, heterogeneity in the pain condition and study methods, and sparse data.

Authors' conclusions

There was only very low quality evidence that oxycodone (as oxycodone MR) is of value in the treatment of painful diabetic neuropathy or postherpetic neuralgia. There was no evidence for other neuropathic pain conditions. Adverse events typical of opioids appeared to be common.

PLAIN LANGUAGE SUMMARY

Oxycodone for neuropathic pain in adults

Bottom line

There is no good evidence that oxycodone works in pain from diabetic neuropathy or postherpetic neuralgia. No studies have reported its use in other types of neuropathic pain.

Background

Neuropathic pain is pain coming from damaged nerves. It is different from pain messages that are carried along healthy nerves from damaged tissue (eg a fall or cut, or arthritic knee). Neuropathic pain is often treated by different medicines (drugs) to those used for pain from damaged tissue, which we often think of as painkillers. For example, medicines that are used to treat depression or epilepsy (fits) can be very effective in some people with neuropathic pain. But sometimes opioid painkillers are used to treat neuropathic pain.

Opioid painkillers are drugs like morphine. Morphine is derived from plants, but many opioids are also made by chemical synthesis rather than being extracted from plants. Oxycodone is a semi-synthetic opioid, manufactured from the opioid alkaloid thebaine.

This review is part of an update of an earlier review, *Oxycodone for neuropathic pain and fibromyalgia in adults*, that has now been split into separate reviews for the two conditions. This review focuses only on neuropathic pain.

Study characteristics

In December 2015, we updated searches from an earlier Cochrane review to look for clinical trials that used oxycodone to treat neuropathic pain in adults. We found two additional studies to include. The earlier review included three studies that compared oxycodone with placebo over several weeks, and the additional studies added oxycodone to existing treatment with pregabalin or gabapentin. Most of the 687 people in the studies had painful limbs because of damaged nerves caused by diabetes.

Key results

Only very low quality evidence suggested that oxycodone relieved the pain. Compared with placebo, fewer people stopped taking oxycodone because they felt it was not effective, but more people experienced side effects.

Quality of the evidence

We rated the quality of the evidence for both benefit and harm as very low because of small numbers of studies and participants, the outcomes reported, and potential bias from the way the studies were analysed. Very low quality evidence means that we are very uncertain about the results.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Oxycodone MR compared with placebo for neuropathic pain

Oxycodone MR compared with placebo for neuropathic pain

Patient or population: adults with neuropathic pain (2 studies in peripheral diabetic neuropathy and 1 study in postherpetic neuralgia)

Settings: community

Intervention: oxycodone MR, 37 to 80 mg daily

Comparison: placebo

Outcomes	Probable outcome with intervention	Probable outcome with comparator	RR, NNT, NNH (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
'Substantial benefit' (≥ 50% reduction in pain or PGIC very much improved)	No data	No data	-	-	Very low	No data
'Moderate benefit' (≥ 30% reduction in pain or PGIC much or very much improved)	440 in 1000	270 in 1000	RR 1.7 (1.3 to 2.1) NNT 5.7 (4.0 to 9.9)	3 studies, 537 participants (587 treatment phases, due to cross-over study), 209 events	Very low	Downgraded 1 level due to potential bias from imputation or completer analysis, 1 level due to heterogeneity in participant pain condition and study methods[a], and 1 level due to small number of studies and events
Withdrawals due to adverse events	130 in 1000	52 in 1000	RR 2.4 (1.5 to 4.0)	5 studies, 680 participants (775 treatment phases due to cross-over studies), 69 events	Very low	Downgraded 1 level due to potential bias from completer analysis, 1 level due to heterogeneity in participant pain condition and study methods[b], and 1 level due to modest number of studies and small number of events
Withdrawals due to lack of efficacy	210 in 1000	100 in 1000	RR 0.20 (0.10 to 0.44) NNH 12 (8.8 to 21)	5 studies, 680 participants (775 treatment phases, due to cross-over studies), 47 events	Very low	Downgraded 1 level due to potential bias from completer analysis, 1 level due to heterogeneity in participant pain condition and study methods[b], and 1 level due to modest number of studies and small number of events

Serious adverse events	44 in 1000	54 in 1000	RR 0.82 (0.37 to 1.82)	4 studies, 352 participants (447 treatment phases due to cross-over studies), 22 events	Very low	Downgraded 1 level due to potential bias from completer analysis, 1 level due to heterogeneity in participant pain condition and study methods[b], and 1 level due to modest number of studies and small number of events
Death	1 event	0 events	-	5 studies, 680 participants (775 treatment phases, due to cross-over studies), 1 event	Very low	Only a single event, and not judged related to study medication

CI: confidence interval; MR: modified release; NNH: number needed to treat for one additional harmful outcome; NNT: number needed to treat for one additional beneficial outcome; PGIC: Patient Global Impression of Change; RR: risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

a: monotherapy or add-on therapy, parallel or cross-over design, some uncertainty about precise outcome used
b: monotherapy or add-on therapy, oxycodone ± naloxone, placebo or 'active placebo', parallel or cross-over design

BACKGROUND

This review is part of an update of an earlier review, 'Oxycodone for neuropathic pain and fibromyalgia in adults' (Gaskell 2014), that has now been split into separate reviews for the two conditions. This review focuses on neuropathic pain and is based on a template for reviews of drugs used to relieve neuropathic pain. The aim is for all reviews to use the same methods, based on new criteria for what constitutes reliable evidence in chronic pain (Moore 2010a; Appendix 1).

Description of the condition

The 2011 International Association for the Study of Pain definition of neuropathic pain is "pain caused by a lesion or disease of the somatosensory system" (Jensen 2011), based on an earlier consensus meeting (Treede 2008). Neuropathic pain is a consequence of a pathological maladaptive response of the nervous system to 'damage' from a wide variety of potential causes. It is characterised by pain in the absence of a noxious stimulus and may be spontaneous (continuous or paroxysmal) in its temporal characteristics or be evoked by sensory stimuli (dynamic mechanical allodynia where pain is evoked by light touch of the skin). Neuropathic pain is almost always associated with a variety of sensory loss (numbness) and sensory gain (allodynia) clinical phenomena, the exact pattern of which vary between patient and disease, perhaps reflecting different pain mechanisms operating in an individual patient and therefore potentially predictive of response to treatment (Demant 2014; Helfert 2015; von Hehn 2012). Pre-clinical research hypothesises a bewildering array of possible pain mechanisms that may operate in people with neuropathic pain, which largely reflect pathophysiological responses in both the central and peripheral nervous systems, including neuronal interactions with immune cells (Baron 2012; Calvo 2012; von Hehn 2012). Overall, even the most effective of available drugs provide only modest benefit in treating neuropathic pain (Finnerup 2015; Moore 2014a), and a robust classification of neuropathic pain is not yet available (Finnerup 2013).

Neuropathic pain is usually divided according to the cause of nerve injury. There may be many causes, but common causes of neuropathic pain include diabetes (painful diabetic neuropathy (PDN)), shingles (postherpetic neuralgia (PHN)), amputation (phantom limb pain), neuropathic pain after surgery or trauma, stroke or spinal cord injury, trigeminal neuralgia, and human immunodeficiency virus (HIV) infection. Sometimes the cause is not known.

Many people with neuropathic pain conditions are significantly disabled with moderate or severe pain for many years. Chronic pain conditions comprised 5 of the 11 top-ranking conditions for years lived with disability in 2010 (Vos 2012), and are responsible for considerable loss of quality of life, employment, and increased healthcare costs (Moore 2014b).

In systematic reviews, the overall prevalence of neuropathic pain in the general population is reported to be between 7% and 10% (van Hecke 2014), and about 7% in a systematic review of studies published since 2000 (Moore 2014b). In individual countries, prevalence rates have been reported as 3.3% in Austria (Gustorff 2008), 6.9% in France (Bouhassira 2008), and up to 8% in the UK (Torrance 2006). Some forms of neuropathic pain, such as PDN and post-surgical chronic pain (which is often neuropathic in origin), are increasing (Hall 2008). The prevalence of PHN is likely to fall if vaccination against the herpes virus becomes widespread.

Estimates of incidence vary between individual studies for neuropathic pain associated with particular conditions, often because of small numbers of cases. In primary care in the UK between 2002 and 2005, the incidences (per 100,000 person-years' observation) were 28 (95% confidence interval (CI) 27 to 30) for PHN, 27 (26 to 29) for trigeminal neuralgia, 0.8 (0.6 to 1.1) for phantom limb pain, and 21 (20 to 22) for PDN (Hall 2008). Others have estimated an incidence of 4 in 100,000 per year for trigeminal neuralgia (Katusic 1991; Rappaport 1994), and of 12.6 per 100,000 person-years for trigeminal neuralgia and 3.9 per 100,000 person-years for PHN in a study of facial pain in the Netherlands (Koopman 2009).

Neuropathic pain is difficult to treat effectively, with only a minority of individuals experiencing a clinically relevant benefit from any one intervention. A multidisciplinary approach is now advocated, with pharmacological interventions being combined with physical or cognitive interventions, or both. Conventional analgesics are usually thought to be ineffective, but without evidence to support or refute that view. Some people with neuropathic pain may derive some benefit from a topical lidocaine patch or low concentration topical capsaicin, though evidence about benefits is uncertain (Derry 2012; Derry 2014). High concentration topical capsaicin may benefit some people with PHN (Derry 2013). Treatment for neuropathic pain is more usually with so-called unconventional analgesics (pain modulators), for example with antidepressants such as duloxetine and amitriptyline (Lunn 2014; Moore 2012a; Sultan 2008), or antiepileptics such as gabapentin or pregabalin (Moore 2009; Moore 2014c; Wiffen 2013).

In clinical trials, the proportion of people who achieve worthwhile pain relief (typically at least 50% pain intensity reduction; Moore 2013a) with any one intervention is small, generally only 10% to 25% more than with placebo, with numbers needed to treat for an additional beneficial outcome (NNT) usually between 4 and 10 (Kalso 2013; Moore 2014a). The proportion in clinical practice is likely to be lower, particularly with opioids, because clinical trials typically exclude people with important physical and mental co-morbidities that have an influence on the pain experience. Neuropathic pain is not particularly different from other chronic pain conditions in that only a small proportion of trial participants have a good response to treatment (Moore 2014a).

The current National Institute for Health and Care Excellence (NICE) guidance for the pharmacological management of neuropathic pain suggests offering "a choice of amitriptyline, duloxetine, gabapentin, or pregabalin as initial treatment for neuropathic pain (with the exception of trigeminal neuralgia)", with switching if first, second, or third drugs tried are not effective or not tolerated (NICE 2013). This concurs with other recent guidance (Finnerup 2015).

Description of the intervention

Oxycodone is a strong opioid agonist, developed in the early 20th century, and chemically related to codeine (Olkkola 2013). It is considered to be comparable to morphine for efficacy, and similar for adverse events, with the exception of hallucinations, which tend to occur rarely with oxycodone (Poyhia 1993). Like morphine, it can be administered via a variety of routes including oral or rectal, and intramuscular, intravenous, or subcutaneous injection.

Its analgesic potency makes it useful for the management of severe pain, usually acute postoperative, post-traumatic, or cancer pain. In acute postoperative pain, oxycodone 15 mg alone compared with placebo, had an NNT for at least 50% pain relief of 4.6 (2.9 to 11) (Gaskell 2009).

A modified-release (MR) oral formulation has been developed for twice-daily dosing in chronic conditions. This formulation may be referred to as controlled-release or prolonged-release oxycodone. The peak plasma concentration is reached in about three hours, compared with one hour for the standard formulation.

Various strands of evidence, mainly from studies in rodents, indicate that oxycodone may exert its opioid effects through the mu-opioid receptor and the kappa-opioid receptor (Kalso 2007). Oral oxycodone is widely used to treat cancer pain where it has similar efficacy to other opioids (Schmidt-Hansen 2015). It is sometimes use to treat chronic non-cancer pain. Individual titration of dose to effect is indicated, especially in older people, as pharmacokinetics may be age-dependent and highly individual (Olkkola 2009).

Repeated administration of oxycodone can cause physical dependence and tolerance. Its potential for abuse is well known, and some reformulation to prevent crushing may reduce this (Butler 2013). Regulation of supply varies between countries, but in many, all oxycodone preparations are controlled substances. There are other general concerns about long-term use of opioids, cognitive impairment and immune and endocrine effects (Brennan 2013), as well as mortality (Dhalla 2009).

How the intervention might work

Opioids such as oxycodone bind to specific opioid receptors in the nervous system and other tissues; there are three principal classes of receptors (mu, kappa, and delta) though others have been suggested, and subtypes of receptors are considered to exist. Binding of opioid agonists like oxycodone to receptors brings about complex cellular changes, outcomes of which include decreased perception of pain, decreased reaction to pain, and increased pain tolerance. Opioids from plant sources have been used for thousands of years to treat pain, and oxycodone has been used since the early 20th century.

Why it is important to do this review

One UK survey found that weak and strong opioids were used frequently for treating neuropathic pain (Hall 2013). Since the early 2000s, a marked increase in prescribing of opioids for non-cancer pain in general, despite a relatively modest evidence base, has in some countries been associated with widespread diversion with consequent abuse, misuse, and mortality. Concurrently, suspicion has arisen that opioid-induced hyperalgesia, together with tolerance to the analgesic effects of opioids, may in reality result in a lesser degree of pain relief from opioids in neuropathic pain than previously assumed. Ballantyne et al suggest that acute and end-of-life pain tend to respond well to opioids and follow a predictable course, but that chronic pain is different and not well managed with opioids (Ballantyne 2016). Furthermore, a cohort study showed that people with neuropathic pain who were prescribed opioids over a 12-month period had worse disability and physical functioning scores than those who were not prescribed opioids, after adjusting for disease severity (Bostick 2015).

The standards used to assess evidence in chronic pain trials have evolved substantially in recent years, with particular attention being paid to trial duration, withdrawals, and statistical imputation following withdrawal, all of which can substantially alter estimates of efficacy. The most important change is the move from using mean pain scores, or mean change in pain scores, to the number of people who have a large decrease in pain (by at least 50%) and who continue taking the treatment, ideally in trials of eight to 12 weeks' duration or longer. Pain intensity reduction of 50% or more correlates with improvements in co-morbid symptoms, function, and quality of life. These standards are set out in the Cochrane Pain, Palliative and Supportive Care Group (PaPaS) Author and Referee Guidance for pain studies (PaPaS 2012).

This Cochrane review assessed evidence using methods that make both statistical and clinical sense, and used developing criteria for what constitutes reliable evidence in chronic pain (Moore 2010a). For inclusion and analysis, trials had to meet a minimum of reporting quality (blinding, randomisation), validity (duration, dose and timing, diagnosis, outcomes, etc), and size (ideally at least 500 participants in a comparison in which the NNT was 4 or above; Moore 1998). This approach sets high standards for the demonstration of efficacy and marks a departure from how reviews were conducted previously.

Taking this newer, more rigorous approach is particularly important for opioids in chronic non-cancer pain. Opioids in clinical trials in non-cancer pain are associated with very high withdrawal rates of up to 60% over about 12 weeks (Moore 2010b). Many withdrawals occur within the first few weeks, when people experience pain relief but cannot tolerate the drug. The common practice of using the last observed results carried forward to the end of the trial many weeks later (last observation carried forward (LOCF)) can, therefore, produce results based largely on people who are no longer in the trial, and who in the real world could not achieve pain relief because they could not take the tablets. The newer standards, outlined in Appendix 1, would not allow this and can produce very different results. For example, one large analysis of pooled data from trials in osteoarthritis and chronic low back pain conducted over about 12 weeks judged oxycodone effective, but an analysis of the same data using the new clinically meaningful standards showed it to be significantly worse than placebo (Lange 2010).

A previous Cochrane review demonstrated the limitations of our knowledge about opioids in neuropathic pain, except in short duration studies of 24 hours or less (McNicol 2013). This was backed up by the earlier version of this review (Gaskell 2014), which found only three studies involving about 250 participants. An update to identify any new evidence for oxycodone, one of the most widely used opioids, is timely.

OBJECTIVES

To assess the analgesic efficacy and adverse events of oxycodone for chronic neuropathic pain in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies if they were randomised controlled trials (RCTs) with at least 10 participants per treatment arm and reported

double-blind assessment of participant outcomes following two weeks of treatment or longer, although the emphasis of the review was on studies of eight weeks or longer. We required full journal publication, with the exception of online clinical trial results, summaries of otherwise unpublished clinical trials, and abstracts with sufficient data for analysis. We did not include short abstracts (usually meeting reports). We excluded studies that were non-randomised, studies of experimental pain, case reports, and clinical observations.

Types of participants

Studies had to include adults aged 18 years and older with one or more chronic neuropathic pain condition including (but not limited to):

- cancer-related neuropathy;
- central neuropathic pain;
- complex regional pain syndrome (CRPS) Type ll;
- human immunodeficiency virus (HIV) neuropathy;
- painful diabetic neuropathy (PDN);
- phantom limb pain;
- postherpetic neuralgia (PHN);
- postoperative or traumatic neuropathic pain;
- spinal cord injury;
- trigeminal neuralgia.

We would have included studies of participants with more than one type of neuropathic pain, with analysis according to the primary condition, but the included studies each enrolled participants with only one pain condition.

Types of interventions

Oxycodone at any dose, by any route, administered for the relief of neuropathic pain and compared with placebo or any active comparator. In this update, we included studies using oxycodone combined with naloxone (to reduce abuse potential and constipation) and also studies using oxycodone as an add-on to stable, but inadequate, treatment with another class of drug (see Differences between protocol and review).

Types of outcome measures

We anticipated that studies would use a variety of outcome measures, with the majority of studies using standard subjective scales (numerical rating scale (NRS) or visual analogue scale (VAS)) for pain intensity or pain relief, or both. We were particularly interested in Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) definitions for moderate and substantial benefit in chronic pain studies (Dworkin 2008). These are defined as:

- at least 30% pain relief over baseline (moderate);
- at least 50% pain relief over baseline (substantial);
- much or very much improved on Patient Global Impression of Change scale (PGIC; moderate);
- very much improved on PGIC (substantial).

These outcomes are different from those used in many earlier reviews, concentrating as they do on dichotomous outcomes where pain responses do not follow a normal (Gaussian) distribution. People with chronic pain desire high levels of pain relief, ideally more than 50% pain intensity reduction, and ideally having no worse than mild pain (Moore 2013a; O'Brien 2010).

Primary outcomes

- Participant-reported pain intensity reduction of 30% or greater.
- Participant-reported pain intensity reduction of 50% or greater.
- PGIC much or very much improved.
- PGIC very much improved.

We planned to analyse data for pain intensity reduction (moderate or substantial) preferentially and separately from data for global impression of change (moderate or substantial), but where there were too few data we would combine data from the different measures for each level of response.

Secondary outcomes

- Any pain-related outcome indicating some improvement.
- Withdrawals due to lack of efficacy and adverse events.
- Participants experiencing any adverse event.
- Participants experiencing any serious adverse event. Serious adverse events typically include any untoward clinical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an 'important medical event' that may jeopardise the person, or may require an intervention to prevent one of the above characteristics or consequences.
- Specific adverse events, particularly somnolence and dizziness.

Search methods for identification of studies

Electronic searches

For this update we searched the following databases, without language restrictions.

- Cochrane Central Register of Controlled Trials (CENTRAL, via the Cochrane Register of Studies Online database (CRSO)) to 21 December 2015.
- MEDLINE (via Ovid) from January 2013 to 21 December 2015.
- EMBASE (via Ovid) from January 2013 to 21 December 2015.

The search strategies for CENTRAL, MEDLINE, and EMBASE are listed in Appendix 2, Appendix 3, and Appendix 4, respectively.

We carried out additional searches for studies using oxycodone plus naloxone, published before January 2013, since these would not have been included in the earlier review.

Searching other resources

We reviewed the bibliographies of any RCTs identified and review articles, and searched clinical trial databases (ClinicalTrials.gov) and World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) to identify additional published or unpublished data. We did not contact study sponsors, but did write to the authors of one study, identified in Clinicaltrials.gov and as a meeting abstract, to ask when results are likely to be available.

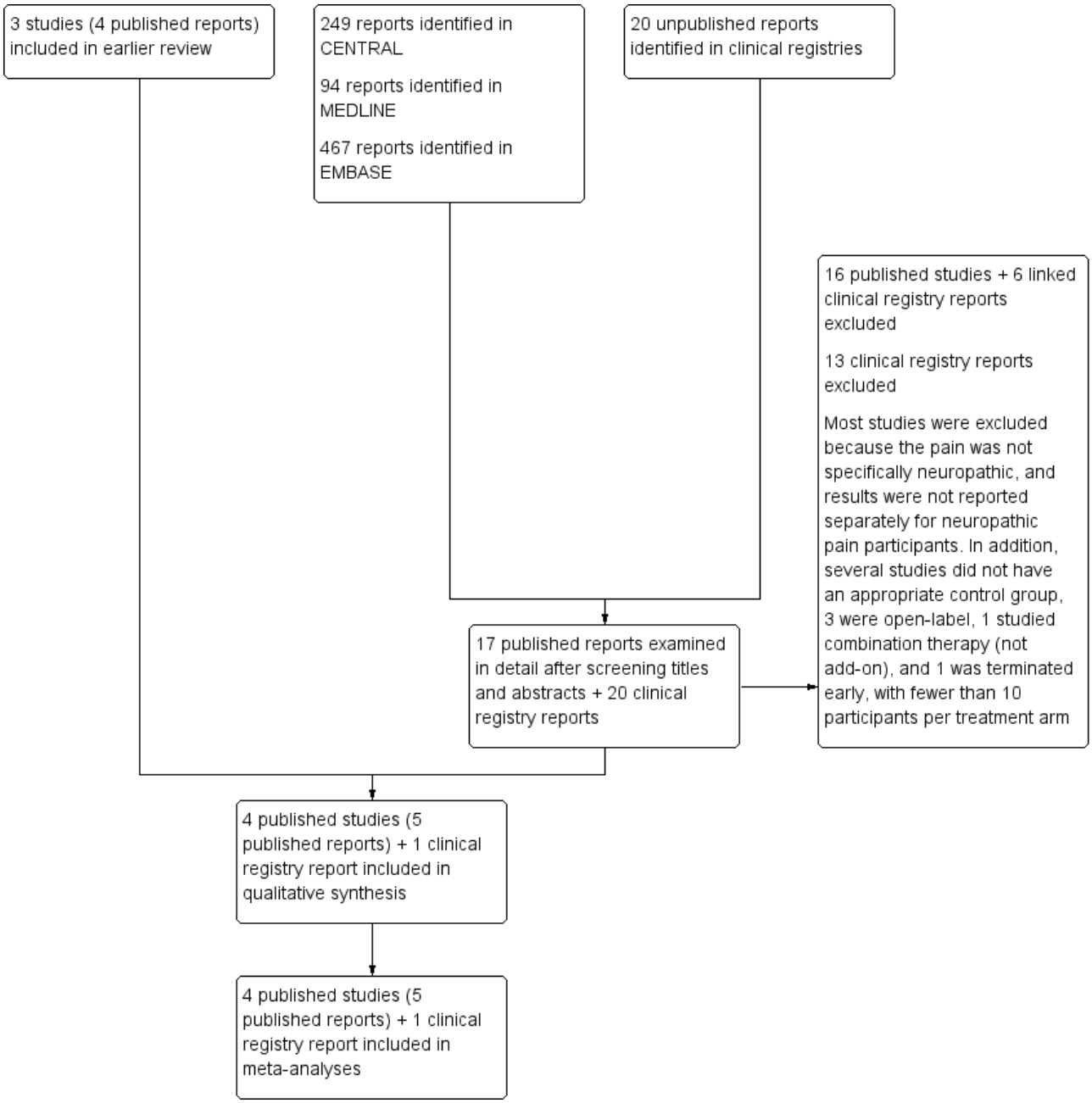
Data collection and analysis

We planned to perform separate analyses for efficacy, according to particular neuropathic pain conditions, and to combine different neuropathic pain conditions for exploratory purposes only. Given the small amount of data available, we combined information from different conditions for exploratory purposes.

Selection of studies

We determined eligibility by reading the abstract of each study identified by the search. We eliminated studies that clearly did not satisfy the inclusion criteria, and obtained full copies of the remaining studies. Two review authors read these studies independently and reached agreement about inclusion by discussion. We did not anonymise the studies in any way before assessment. We included a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart (Figure 1).

Figure 1. Study flow diagram.



Data extraction and management

Two review authors independently extracted data using a standard form and checked for agreement before entry into Review Manager 5 (RevMan 2014) or any other analysis tool. We included information about the pain condition and number of participants treated, drug and dosing regimen, study design (placebo or active control), study duration and follow-up, analgesic outcome measures and results, withdrawals, and adverse events (participants experiencing any adverse event or serious adverse event).

Assessment of risk of bias in included studies

We used the Oxford Quality Score (Jadad 1996) as the basis for inclusion, limiting inclusion to studies that, as a minimum, were randomised and double-blind.

Two review authors independently assessed risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), and adapted from those used by the Cochrane Pregnancy and Childbirth Group, with any disagreements resolved by discussion. We assessed the following for each study.

- Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, eg random number table; computer random number generator); unclear risk of bias (method used to generate sequence was not clearly stated). We excluded studies using a non-random process, which were therefore at high risk of bias (eg odd or even date of birth; hospital or clinic record number).
- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions before assignment determines whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (eg telephone or central randomisation; consecutively numbered, sealed, opaque envelopes); unclear risk of bias (method was not clearly stated). We excluded studies that did not conceal allocation and were therefore at high risk of bias (eg open list).
- Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding, eg identical tubes containing gel, or identical plasters; matched in appearance and smell); unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how blinding was achieved). We excluded studies that were not double-blind and therefore at high risk of bias.
- Incomplete outcome data (checking for possible attrition bias due to the amount, nature, and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk of bias (less than 10% of participants did not complete the study or used 'baseline observation carried forward' (BOCF) analysis, or both); unclear risk of bias (used LOCF analysis); or high risk of bias (used 'completer' analysis).
- Size (checking for possible biases confounded by small size). Small studies have been shown to overestimate treatment effects, probably due to methodological weaknesses (Dechartres 2013; Nüesch 2010). We assessed studies as at low risk of bias if they had at least 200 participants per treatment arm, at unclear risk if they had 50 to 200 participants per treatment arm, and at high risk if they had fewer than 50 participants per treatment arm.

Measures of treatment effect

We calculated NNTs as the reciprocal of the absolute risk reduction (McQuay 1998). For unwanted effects, the NNT becomes the NNH and is calculated in the same manner. We used dichotomous data to calculate risk ratio (RR) with 95% confidence intervals (CI) using a fixed-effect model. In the event of significant statistical heterogeneity, we would consider using a random-effects model (see Assessment of heterogeneity). We did not plan to use continuous data in analyses.

Unit of analysis issues

We accepted randomisation to individual participant only. In the event of a study having more than one active treatment arm, in which data were not combined for analysis, we planned to split the control treatment arm between active treatment arms. For cross-over studies, we planned to use only the first period, if this was available. Where only combined data for both periods were reported, we treated the study as if it was a parallel study, drawing attention to the potential bias that this confers, and interpreting the results accordingly.

Dealing with missing data

We used intention-to-treat (ITT) analysis where the ITT population consisted of participants who were randomised, took at least one dose of the assigned study medication, and provided at least one post-baseline assessment. We assigned zero improvement to missing participants wherever possible. We have commented where ITT data were not available.

Assessment of heterogeneity

We planned to deal with clinical heterogeneity by combining studies that examined similar conditions, and to assess statistical heterogeneity visually (L'Abbé 1987) and with the use of the I^2 statistic. When the I^2 value was greater than 50%, we considered possible reasons for this.

Assessment of reporting biases

The aim of this review was to use dichotomous data of known utility and of value to people with pain (Hoffman 2010; Moore 2010c; Moore 2010d; Moore 2010e; Moore 2013a). The review did not depend on what authors of the original studies chose to report or not report, although clearly difficulties arose where studies did not to report dichotomous results of interest. We extracted continuous data, which probably poorly reflect efficacy and utility, where useful, for illustrative purposes only.

We assessed publication bias using a method designed to detect the amount of unpublished data with a null effect that would be required to make the result of any efficacy analysis clinically irrelevant (usually taken to mean an NNT of 10 or more in these conditions) (Moore 2008).

Data synthesis

We planned to analyse individual painful conditions separately because placebo response rates with the same outcome can vary between conditions, as can the drug-specific effects (Moore 2009). This was not possible because there were very limited data. We used a fixed-effect model for meta-analysis, and analysed data in three tiers, according to outcome and freedom from known sources of bias.

- The first tier uses data meeting current best standards, where studies report the outcome of at least 50% pain intensity reduction over baseline (or its equivalent), without the use of LOCF or other imputation methods for drop-outs, report an ITT analysis, last eight weeks or more, have a parallel group design, and have at least 200 participants (preferably at least 400) in the comparison (Moore 1998; Moore 2010a; Moore 2012b).
- The second tier uses data from at least 200 participants but where one or more of the above conditions is not met (eg reporting at least 30% pain intensity reduction, using LOCF or a completer analysis, or lasting four to eight weeks).
- The third tier of evidence relates to data from fewer than 200 participants, or where there are expected to be significant problems because, for example, of very short duration studies of less than four weeks, where there is major heterogeneity between studies, or where there are shortcomings in allocation concealment, attrition, or incomplete outcome data. For this third tier of evidence, no data synthesis is reasonable, and may be misleading, but an indication of beneficial effects might be possible.

In the event, because there were so few data, we chose to pool results for different conditions in exploratory analyses for efficacy, adverse events, and withdrawals.

Quality of the evidence

Two review authors independently rated the quality of each outcome. We used the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system to assess the quality of the evidence related to the key outcomes listed in Types of outcome measures, as appropriate (Higgins 2011b; Appendix 5).

'Summary of findings' table

We included a 'Summary of findings' table, as set out in the author guide (PaPaS 2012), to present the main findings in a transparent and simple tabular format. We included key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the outcomes of 'substantial benefit' (at least 50% pain intensity reduction, or PGIC very much improved), 'moderate benefit' (at least 30% pain intensity reduction, or PGIC much or very much improved), withdrawals due to adverse events, withdrawals due to lack of efficacy, serious adverse events, and death (Summary of findings for the main comparison).

Subgroup analysis and investigation of heterogeneity

We planned to analyse separately data for different pain conditions and dosing regimens, but this was not possible.

For this update, we included studies using oxycodone as an add-on therapy and studies using oxycodone in combination with naloxone, and chose to analyse these studies as a separate subgroup to investigate potential heterogeneity.

Sensitivity analysis

No sensitivity analyses were planned, but because we combined data from the study in PHN with those in diabetic neuropathy for this update, we carried out sensitivity analyses (where there were sufficient data) to determine the effect of excluding PHN. In addition, because one study used an 'active' placebo, we carried out sensitivity analyses (where there were sufficient data) to determine whether this had any effect on the incidence of adverse events.

RESULTS

Description of studies

Results of the search

The earlier review included three studies (four reports) and excluded 14 studies. Updated searches identified 249 studies in CENTRAL, 94 in MEDLINE, and 467 in EMBASE. After screening titles and abstracts, we obtained full copies of 17 studies. We also identified a further 20 studies in clinical trial registries, of which we linked six to published studies and the remaining 14 appeared to be unpublished. Only one additional published study and one trial registry report satisfied our inclusion criteria (Hanna 2008; NCT00944697). See Figure 1.

Included studies

We included five studies, with 687 participants randomised to treatment with oxycodone, oxycodone plus naloxone, or placebo (Gimbel 2003; Hanna 2008; NCT00944697; Watson 1998; Watson 2003). Another report from Jensen et al described additional results from the study by Gimbel 2003. Both newly included studies in this update added treatment with oxycodone to established, stable, but inadequate treatment with either gabapentin (Hanna 2008) or pregabalin (NCT00944697). Participants took oral oxycodone MR for up to four (Watson 1998; Watson 2003), six (Gimbel 2003), or 12 weeks (Hanna 2008), or the combination of oxycodone plus naloxone for 12 weeks (NCT00944697).

Studies enrolled participants who had experienced at least moderate pain for three months or more, associated with either PHN (Watson 1998) or diabetic neuropathy (painful symmetrical distal polyneuropathy) in people with stable diabetes (Gimbel 2003; Hanna 2008; NCT00944697; Watson 2003). There were no included studies of oxycodone for neuropathic pain of other aetiology. The mean age of participants ranged between 59 and 70 years, with no upper age limits, and there were similar numbers of men and women. Study recruitment was from a chronic pain specialist or through newspaper advertising in one study (Watson 1998); from primary, secondary, and tertiary care in one study (NCT00944697); and not reported in the other studies. Three studies were multicentred (Gimbel 2003; Hanna 2008; NCT00944697). Chronic pain of other aetiology, a history of substance or alcohol abuse, or both, were specific exclusion criteria in Gimbel 2003; Watson 1998; Watson 2003, and participants in NCT00944697 were opioid naive. The extent of other exclusion criteria varied between studies.

Four studies compared oxycodone MR with a placebo (Gimbel 2003; Hanna 2008; NCT00944697; Watson 1998) or an "active" placebo

(benztropine) (Watson 2003). Three studies used a parallel group design (Gimbel 2003; Hanna 2008; NCT00944697). The other two were cross-over studies, and neither reported data from the first phase separately (Watson 1998; Watson 2003).

All participants discontinued pre-study opioids with an appropriate washout period before the start of the study (except NCT00944697 where they were opioid naive), but other stable medication (eg including for pain and diabetes) was continued unchanged. There was no washout between phases in the two cross-over studies. In Gimbel 2003, Watson 1998 and Watson 2003, the dosage of oxycodone MR was progressively increased to a maximum of 60 to 120 mg daily, taken as a divided dose, and the mean dosages achieved were similar in the three studies (37 to 45 mg daily). Two studies did not report details of daily doses (Hanna 2008; NCT00944697).

We found no relevant studies in chronic neuropathic pain conditions other than PDN or PHN. We identified several studies using a fixed combination of oxycodone and naloxone in chronic non-cancer pain, but all of these included participants with mixed conditions and did not report results for neuropathic pain separately.

Excluded studies

We excluded 29 studies, 13 of which were available only as clinical trial registry reports. Pain was not identified as being specifically, or predominantly, neuropathic in the majority of excluded studies. Reasons for exclusion of individual studies are in the Characteristics of excluded studies table.

Risk of bias in included studies

Figure 2 and Figure 3 illustrate the risk of bias assessments by category for each included study.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

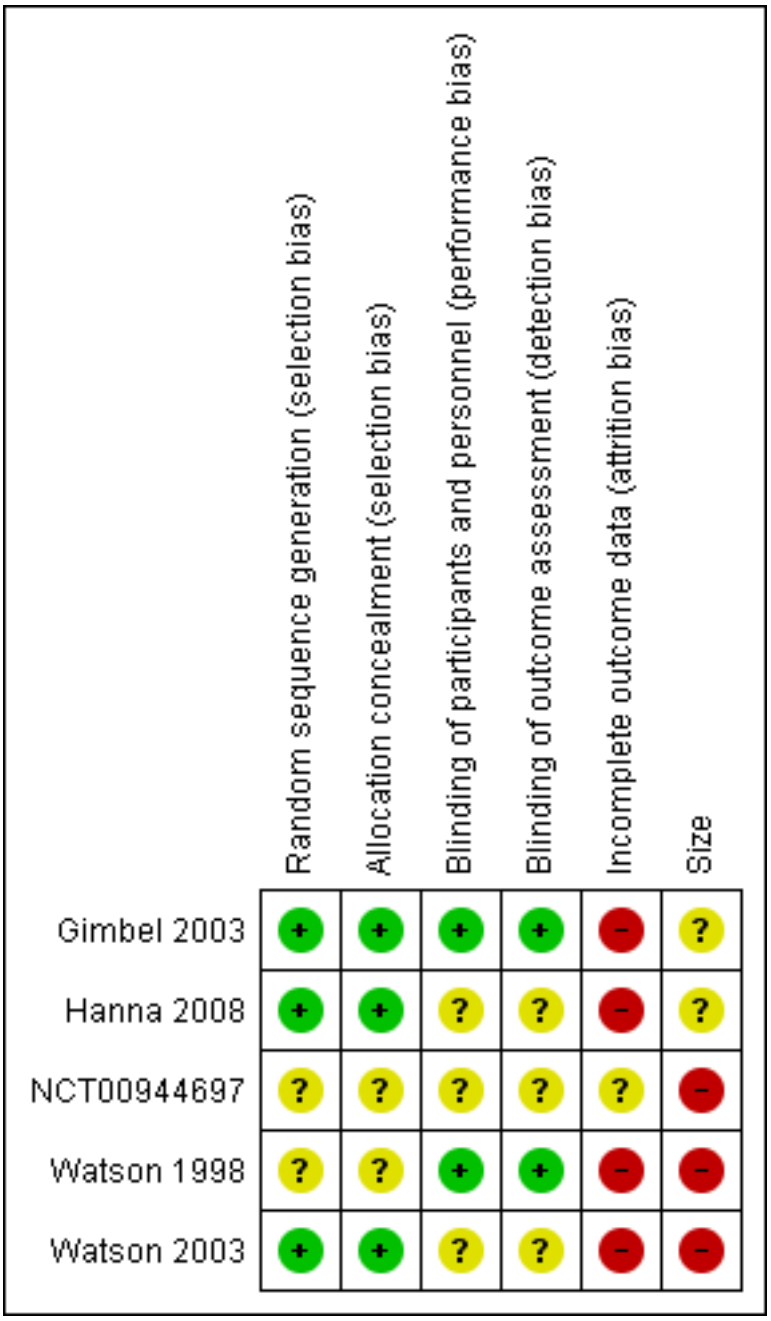
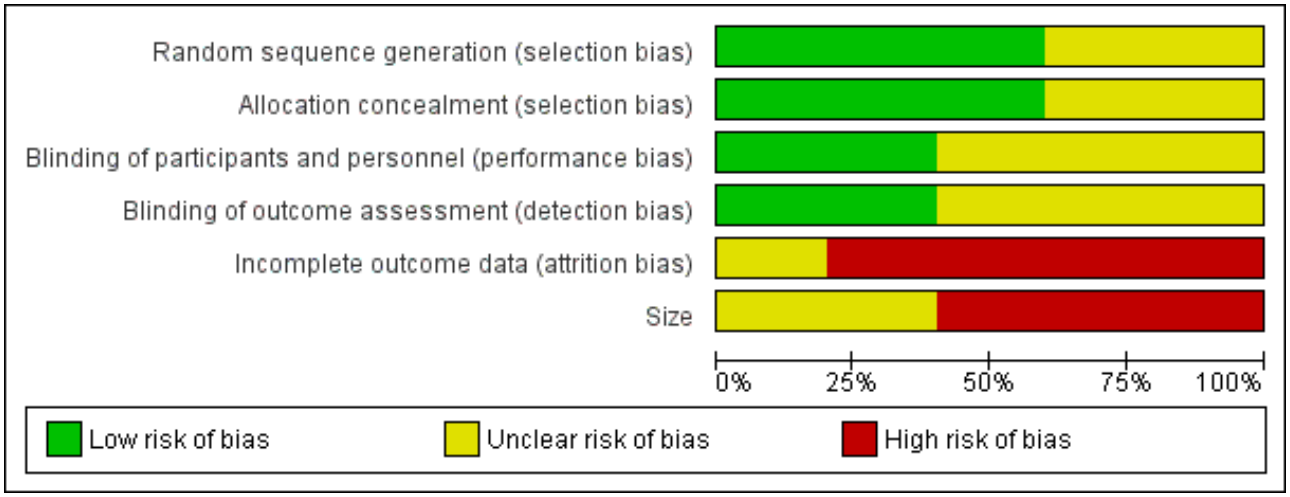


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

All studies were randomised, but two studies did not report the methods used to generate the random sequence and maintain allocation concealment (NCT00944697; Watson 1998). We judged these two studies at unclear risk of bias for these items.

Blinding

All studies were double-blind, but three studies did not report the methods used to achieve double-blinding (Hanna 2008; NCT00944697; Watson 2003). Watson 2003 carried out a "Test of blinding" by participants and investigators at the end of the study, but did not report the details. We judged these three studies at unclear risk of bias for this item.

Incomplete outcome data

Gimbel 2003 reported that they used LOCF for participants who withdrew from the study, and Hanna 2008 used LOCF for missing scores and discontinuation, while Watson 1998 and Watson 2003 reported efficacy data only for participants who provided data for both phases of the cross-over (completer analysis). We judged these studies at high risk of bias for this item. NCT00944697 did not mention how they handled missing data; we judged this as unclear risk.

Other potential sources of bias

None of the studies randomised sufficient numbers of participants to minimise the bias associated with small studies. We judged two studies at unclear risk of bias for this item (Gimbel 2003; Hanna 2008). The remaining studies included, or reported on, fewer than 50 participants per treatment arm (NCT00944697; Watson 2003; Watson 1998); we judged them at high risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Oxycodone MR compared with placebo for neuropathic pain

Efficacy

All included studies reported at least one pain-related outcome indicating some improvement with oxycodone MR compared with placebo, except NCT00944697, which did not show any improvement. There was no first or second tier evidence of efficacy. Appendix 6 provides details of efficacy outcomes for individual studies.

Third tier evidence

None of the included studies reported outcomes equivalent to our prespecified outcome of substantial benefit (pain intensity reduction of 50% or greater, or global impression of clinical change (PGIC) very much improved).

Using a responder analysis with participant-reported pain relief and LOCF imputation, Jensen 2006 (Gimbel 2003) reported that 37/82 participants experienced pain intensity reduction of 33% or greater (equivalent to moderate benefit) for the item "intense pain" with oxycodone MR and 20/77 with placebo. Gimbel 2003 reported a statistically significant difference in change from baseline in three fields in the Brief Pain Inventory (current pain, pain relief, and sleep) after 42 days of treatment. In the ITT population, there was a statistically significant difference in average pain intensity over 28 days of treatment, and also in satisfaction with oxycodone MR compared with placebo over 42 days of treatment. Participants taking oxycodone MR had more days with mild pain than participants taking placebo, and also a lower median time to achieve mild pain.

Hanna 2008 reported a mean reduction of 0.6 'boxes' (points) on an 11 point scale, 2.1 boxes with oxycodone and 1.5 boxes with placebo after 12 weeks of treatment, and claimed this was "equivalent to 33% reduction in pain scores with oxycodone MR plus gabapentin" (moderate benefit). In a global assessment of pain, 72/163 participants taking oxycodone MR reported good or very good responses (moderate benefit), and 51/165 participants taking placebo. The study authors commented that participants who did not complete rated the treatment less favourably.

NCT00944697 reported a mean Short Form McGill Pain Score of 48/150 for oxycodone MR plus naloxone and 50/150 for placebo (high scores = worse pain), indicating no benefit from adding oxycodone MR.

Watson 1998 reported efficacy results only for the 38/50 participants who completed both phases of the cross-over study. The authors reported that 58% of participants treated with oxycodone MR and 18% treated with placebo experienced at least moderate pain relief (at least 3 on a scale of 0 to 5). We assumed that this outcome was derived from weekly assessments of effectiveness of treatment, including ratings of "moderately effective" and "highly effective". Classifying participants who did not complete the study as non-responders (BOCF) gave moderate benefit to 22/50 participants with oxycodone MR and 7/50 participants with placebo. Group mean data showed a statistically significant improvement in pain relief, steady pain, allodynia, and paroxysmal spontaneous pain with oxycodone MR, and global effectiveness and disability were better with oxycodone MR. More participants reported a preference for oxycodone MR than placebo (67% with oxycodone MR versus 11% with placebo, with 22% having no preference).

Watson 2003 reported similar results for both the "evaluable population" and the ITT population. Mean pain intensity and pain relief scores were significantly better with oxycodone MR than with placebo. About 88% of participants preferred oxycodone MR, which was considered at least moderately effective by 95% of participants who completed the study, and 73% said they were satisfied with the treatment. They reported no equivalent data for placebo. They did not report information on the number of participants who experienced at least moderate pain relief (using a non-standard 6-point scale), but the authors did report an NNT for this outcome of 2.6. It is unclear whether this was calculated using the "evaluable population" (who completed both phases of the cross-over) or the ITT population, and it is unclear whether they used any imputation method.

Moderate benefit in painful diabetic neuropathy

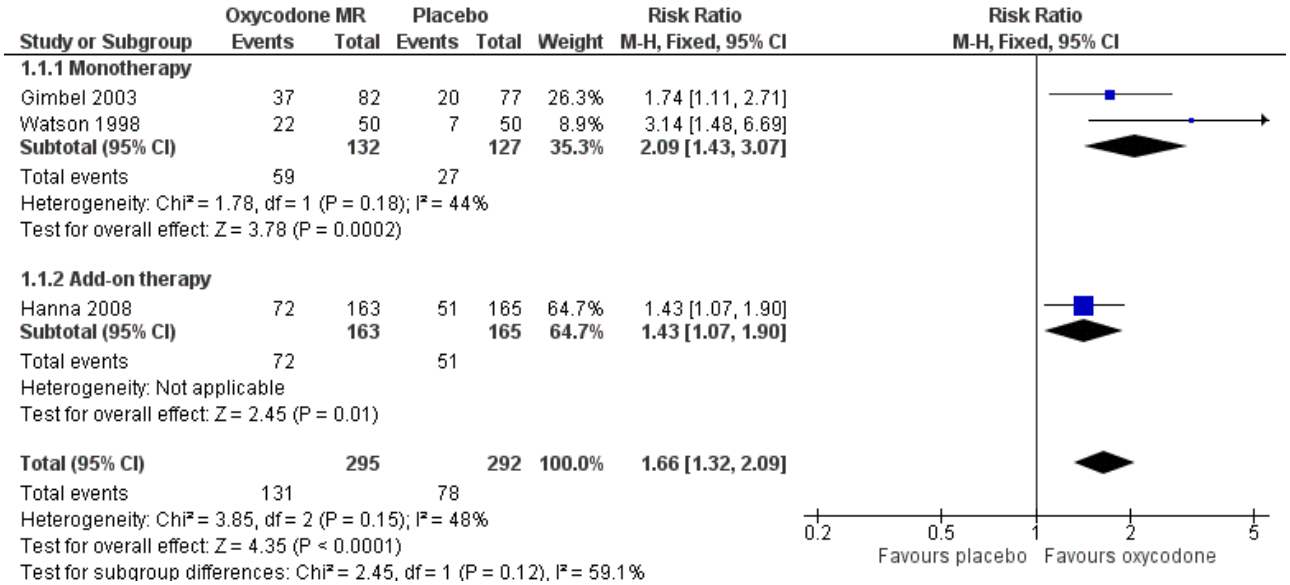
Three studies in 537 participants (50 in a cross-over study) with PDN reported outcomes that, ***as best we could tell*** , approximated to our prespecified outcomes for moderate pain relief. We analysed data as two subgroups (monotherapy (Gimbel 2003; Watson 1998) and add-on therapy (Hanna 2008)). Watson 1998 used a cross-over design without reporting withdrawals by period, and we chose to combine data from this study, as reported, with that from the parallel group study of monotherapy (Gimbel 2003).

Monotherapy

Two studies, with 259 participants, reported the effects of monotherapy on moderate pain relief (Gimbel 2003; Watson 1998).

- The proportion of participants experiencing moderate pain relief with oxycodone MR was 45% (59/132, range 44% to 45%).
- The proportion of participants experiencing moderate pain relief with placebo was 21% (27/127, range 14% to 26%).
- The RR for moderate pain relief with oxycodone MR compared with placebo was 2.1 (95% CI 1.4 to 3.1); the NNT was 4.3 (2.9 to 8.1) (Figure 4).

Figure 4. Forest plot of comparison: 1 Oxycodone MR versus placebo, outcome: 1.1 At least moderate pain relief.



Add-on therapy

Only one study, with 328 participants, reported the effects of add-on therapy on moderate pain relief (Hanna 2008); 72/163 participants experienced moderate pain relief with oxycodone MR and 51/165 with placebo.

All studies

Combining all three studies, 44% (131/295, range 44% to 45%) of participants experienced moderate pain relief with oxycodone MR, and 27% (78/292, range 14% to 31%) with placebo. The RR was 1.7 (1.3 to 2.1) and the NNT was 5.7 (4.0 to 9.9) (Figure 4).

We downgraded the quality of the evidence for this analysis to very low because of the small number of studies and participants,

heterogeneity in study methods, uncertainty over the outcomes as reported, and because of uncertainties in achieving a true ITT denominator. For other efficacy outcomes, there were additional concerns relating to the outcomes reported and the imputation methods used (or methods for imputation were not reported).

Withdrawals

All studies reported withdrawals due to adverse events and lack of efficacy. Details of withdrawals reported in individual studies are in Appendix 7.

We analysed data as two subgroups (monotherapy (Gimbel 2003; Watson 1998; Watson 2003), and add-on therapy (Hanna 2008; NCT00944697)), and for all studies combined. Two of the studies of monotherapy used a cross-over design without reporting withdrawals by period (Watson 1998; Watson 2003), and we chose to combine the analyses from these studies, as reported, with those of the parallel group study of monotherapy (Gimbel 2003). One study used an active placebo (Watson 2003).

We downgraded the quality of the evidence for all withdrawal outcomes to very low due to the small or modest number of studies and events and the exploratory nature of our analyses (mixed neuropathic pain conditions, 'active' placebo in one study).

Withdrawals due to adverse events

Monotherapy

Three studies, with 349 participants, reported the effect of monotherapy on withdrawals due to adverse events (Gimbel 2003; Watson 1998; Watson 2003).

- The proportion of participants who withdrew due to an adverse event with oxycodone MR was 11% (19/177, range 8.5% to 16%).
- The proportion of participants who withdrew due to an adverse event with placebo was 6.4% (11/172, range 5.2% to 11%).
- The RR for withdrawal with oxycodone MR compared with placebo was 1.7 (0.83 to 3.4); the NNH was not calculated (Analysis 1.2).

Sensitivity analyses

Excluding Watson 1998 (PHN) gave an RR of 1.7 (0.74 to 3.9); the NNH was not calculated. The result was not significantly changed.

Excluding Watson 2003 ('active' placebo) gave an RR of 1.7 (0.67 to 4.1); the NNH was not calculated. The result was not significantly changed.

Add-on therapy

Two studies, with 426 participants, reported the effects of add-on therapy on withdrawals due to adverse events (Hanna 2008; NCT00944697).

- The proportion of participants who withdrew due to an adverse event with oxycodone MR was 14% (30/211, range 6% to 17%).
- The proportion of participants who withdrew due to an adverse event with placebo was 4.2% (9/215, range 0% to 5.5%).
- The RR for withdrawal with oxycodone MR compared with placebo was 3.3 (1.6 to 6.6); the NNH was 10 (6.5 to 22) (Analysis 1.2).

All included studies

Combining all five studies, 13% (49/388, range 6% to 17%) of participants withdrew due to an adverse event with oxycodone MR, and 5.2% (20/387, range 0% to 9%) with placebo. The RR was 2.4 (1.5 to 3.9) and the NNH was 13 (8.8 to 29) (Analysis 1.2).

Withdrawals due to lack of efficacy

Monotherapy

Three studies, with 349 participants, reported the effects of monotherapy on withdrawals due to lack of efficacy (Gimbel 2003; Watson 1998; Watson 2003).

- The proportion of participants who withdrew due to lack of efficacy with oxycodone MR was 1.1% (2/177, range 0% to 2.2%).
- The proportion of participants who withdrew due to lack of efficacy with placebo was 11% (19/172, range 2.0% to 16%).
- The RR for withdrawal with oxycodone MR compared with placebo was 0.12 (0.03 to 0.45); the NNTp was 10 (6.7 to 20) (Analysis 1.3).

Sensitivity analysis

Excluding Watson 1998 (PHN) gave an RR of 0.11 (0.03 to 0.45); the NNTp was 7.6 (5.0 to 15). The result was not significantly changed.

Add-on therapy

Two studies, with 426 participants, reported the effects of add-on therapy on withdrawals due to lack of efficacy (Hanna 2008; NCT00944697).

- The proportion of participants who withdrew due to lack of efficacy with oxycodone was 2.8% (6/211, range 0% to 3.7%).
- The proportion of participants who withdrew due to lack of efficacy with placebo was 9.3% (20/215, range 0% to 12%).
- The RR for withdrawal with oxycodone MR compared with placebo was 0.30 (0.13 to 0.74); the NNTp was 15 (9.1 to 51) (Analysis 1.3).

All included studies

Combining all five studies, 2.1% (8/388, range 0% to 4%) of participants withdrew due to lack of efficacy with oxycodone MR, and 10% (39/387, range 0% to 16%) with placebo. The RR was 0.21 (0.10 to 0.44) and the NNTp was 12 (8.8 to 21) (Analysis 1.3).

Adverse events

Appendix 7 details adverse events reported in individual studies. We analysed data as two subgroups (monotherapy (Gimbel 2003; Watson 1998; Watson 2003) and add-on therapy (Hanna 2008; NCT00944697)), and for all studies combined. Two of the studies of monotherapy used a cross-over design without reporting adverse events by period (Watson 1998; Watson 2003), and we chose to combine the analyses from these studies, as reported, with those of the parallel group study of monotherapy (Gimbel 2003). One study used an active placebo (Watson 2003).

We downgraded the quality of the evidence for all adverse event outcomes to very low due to the small or modest number of studies and events and the exploratory nature of our analyses (mixed neuropathic pain conditions, 'active' placebo in one study).

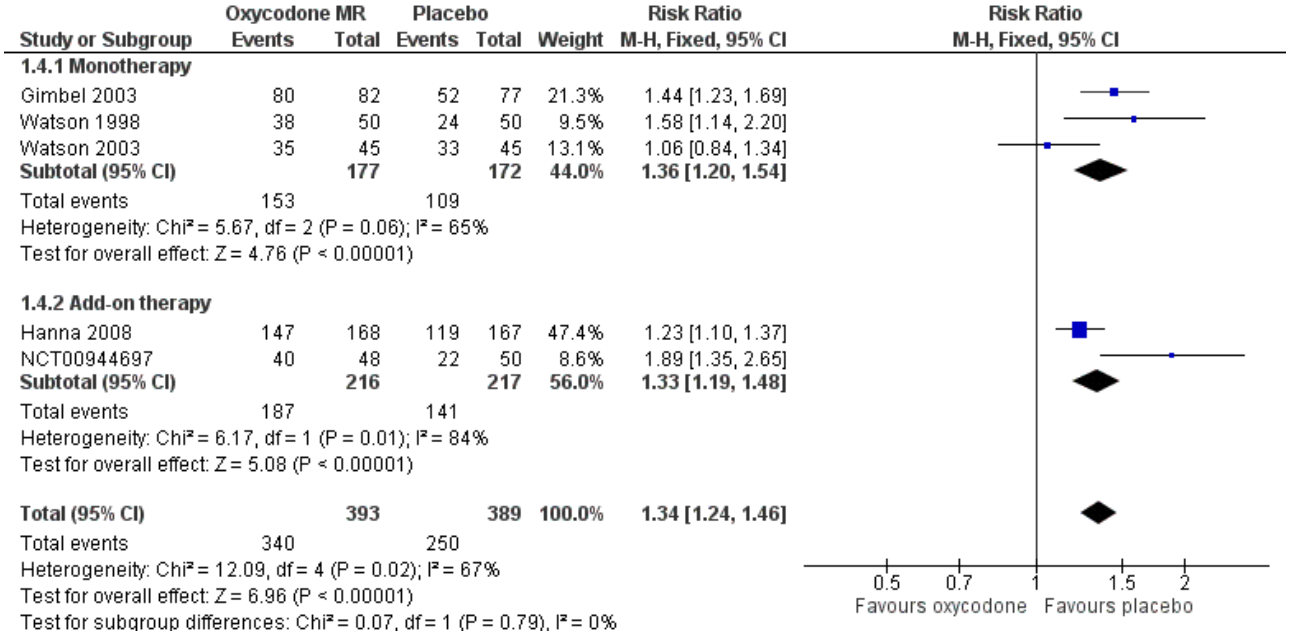
Participants experiencing any adverse event

Monotherapy

Three studies, with 349 participants, reported the effects of monotherapy on experiencing any adverse effects (Gimbel 2003; Watson 1998; Watson 2003).

- The proportion of participants experiencing any adverse event with oxycodone MR was 86% (153/177, range 76% to 98%).
- The proportion of participants experiencing any adverse event with placebo was 63% (109/172, range 48% to 73%).
- The RR for participants experiencing any adverse event with oxycodone MR compared with placebo was 1.4 (1.2 to 1.5); the NNH was 4.3 (3.1 to 7.0) (Figure 5).

Figure 5. Forest plot of comparison: 1 Oxycodone MR versus placebo, outcome: 1.4 Any adverse event.



Sensitivity analyses

Excluding Watson 1998 (PHN) gave an RR of 1.3 (1.1 to 1.5); the NNH was 4.8 (3.3 to 8.9). The result was not significantly changed.

Excluding Watson 2003 ('active' placebo), gave an RR of 1.5 (1.3 to 1.7); the NNH was 3.4 (2.5 to 5.1). The result was not significantly changed.

Add-on therapy

Two studies, with 433 participants, reported the effects of add-on therapy on experiencing any adverse effects (Hanna 2008; NCT00944697).

- The proportion of participants experiencing any adverse event with oxycodone MR was 87% (187/216, range 83% to 88%).
- The proportion of participants experiencing any adverse event with placebo was 65% (141/217, range 44% to 71%).
- The RR for participants experiencing any adverse event with oxycodone MR compared with placebo was 1.3 (1.2 to 1.5); the NNH was 4.6 (3.4 to 7.3) (Figure 5).

All included studies

Combining all five studies, 87% (340/393, range 76% to 98%) of participants experienced adverse events with oxycodone MR, and 64% (250/389, range 44% to 73%) with placebo. The RR was 1.3 (1.2 to 1.5) and the NNH was 4.5 (3.6 to 6.1) (Figure 5).

The I^2 statistic was greater than 50% for each of these analyses, but the direction of effect was constant and the CIs overlapped; the high I^2 statistic was probably due to the small size of the individual studies.

Participants experiencing any serious adverse event

Four studies, with 447 participants, reported on participants experiencing a serious adverse event (Gimbel 2003; NCT00944697; Watson 2003). Although not specifically reported, we have assumed that there were no serious adverse events in Watson 1998. Hanna 2008 reported that some serious adverse events occurred, but none were related to study medication. None of the serious adverse events were judged by the study authors to be linked to taking oxycodone MR.

Monotherapy

Three studies, with 349 participants reported the effects of monotherapy on experiencing any serious adverse event (Gimbel 2003; Watson 1998; Watson 2003).

- The proportion of participants experiencing any serious adverse event with oxycodone MR was 3.4% (6/177, range 0% to 6.1%).
- The proportion of participants experiencing any serious adverse event with placebo was 7.0% (12/172, range 0% to 12%).
- The RR for participants experiencing any serious adverse event with oxycodone MR compared with placebo was 0.48 (0.18 to 1.2); the NNH was not calculated (Analysis 1.5).

We did not carry out sensitivity analyses for this outcome due to the very small number of events.

Add-on therapy

Only one study, with 98 participants, reported the effects of add-on therapy on experiencing any serious adverse event (NCT00944697). There were four serious adverse events with oxycodone MR, and none with placebo.

All included studies

Combining all four studies, 4% (10/225, range 0% to 8%) of participants experienced a serious adverse event with oxycodone MR, and 5% (12/222, range 0% to 12%) with placebo. The RR was 0.82 (0.37 to 1.8); the NNH was not calculated (Analysis 1.5).

Deaths

There was one death in a participant taking oxycodone MR (Gimbel 2003), but was not judged by the study authors to be linked to treatment.

Specific adverse events

Three studies reported specific adverse events fully (584 participants, Gimbel 2003; Hanna 2008; Watson 2003). There were insufficient data to carry out subgroup analysis, or any sensitivity analysis. We pooled the available data for exploratory purposes.

Constipation

- The proportion of participants experiencing constipation with oxycodone MR was 32% (93/295, range 27% to 43%).
- The proportion of participants experiencing constipation with placebo was 8.7% (25/289, range 6.0% to 14%).
- The RR for participants experiencing constipation with oxycodone MR compared with placebo was 3.6 (2.4 to 5.4); the NNH was 4.4 (3.4 to 6.0) (Analysis 1.6).

Nausea

- The proportion of participants experiencing nausea with oxycodone MR was 30% (89/295, range 26% to 36%).
- The proportion of participants experiencing nausea with placebo was 11% (32/289, range 7.8% to 18%).
- The RR for participants experiencing nausea with oxycodone MR compared with placebo was 2.7 (1.9 to 4.0); the NNH was 5.2 (3.9 to 7.9) (Analysis 1.6).

Somnolence

- The proportion of participants experiencing somnolence with oxycodone MR was 27% (79/295, range 20% to 40%).
- The proportion of participants experiencing somnolence with placebo was 7.3% (21/289, range 1.3% to 24%).
- The RR for participants experiencing somnolence with oxycodone MR compared with placebo was 3.7 (2.3 to 5.9); the NNH was 5.1 (3.9 to 7.3) (Analysis 1.6).

Dizziness

- The proportion of participants experiencing dizziness with oxycodone MR was 20% (58/295, range 15% to 32%).
- The proportion of participants experiencing dizziness with placebo was 5.9% (17/289, range 3.6% to 10%).
- The RR for participants experiencing dizziness with oxycodone MR compared with placebo was 3.3 (2.0 to 5.5); the NNH was 7.3 (5.3 to 12) (Analysis 1.6).

Other adverse events affecting at least 8% of participants taking oxycodone MR in some studies included vomiting and pruritus.

DISCUSSION

Summary of main results

The review update found five studies testing oxycodone MR in 687 participants with chronic neuropathic pain due to painful diabetic neuropathy (painful symmetrical distal polyneuropathy) and postherpetic neuralgia. No first or second tier evidence was available. Third tier evidence indicated some improvement in pain relief with oxycodone MR compared with placebo. In three studies that reported outcomes we judged to be equivalent to 'moderate benefit', 44% of participants had moderate benefit with oxycodone MR, and 27% with placebo; the NNT was 5.7 (4.0 to 9.9). Other outcomes reported also indicated some improvement, but this was derived from group mean data, completer analyses, and LOCF (or unspecified) imputation (Appendix 1) in small, mostly short duration studies, where major bias was possible, and where there was some uncertainty over the precise outcome being reported and the true ITT denominator. Participants taking oxycodone MR experienced more adverse events (but not serious adverse events) than did participants taking placebo, and more people withdrew because of adverse events. Constipation, nausea, dizziness, and somnolence, which are typical opioid adverse events, were all more frequent with oxycodone MR than with placebo. One study used an active placebo to help maintain blinding, which influences interpretation of data on adverse events in this case. See Summary of findings for the main comparison.

Overall completeness and applicability of evidence

Overall completeness and applicability of evidence were poor. Oxycodone MR was tested mainly in PDN, and in a small number of participants with PHN; there were no data for other conditions. The usefulness of the available evidence was limited because reporting quality was poor by current standards. Three of the included studies had treatment periods of up to six weeks' duration, but these shorter studies do not necessarily provide information about longer-term use, which is important in the treatment of a chronic condition. In particular, concern has been raised about the lack of evidence on potential problems with long-term use of opioids in the treatment of chronic pain (such as safety issues, addiction, and misuse) (Dworkin 2007; Stannard 2013). There was limited information in the studies on co-morbidities, such as significant renal impairment, which may be relevant in clinical practice.

In addition, the use of LOCF imputation may well result in overestimation of treatment effect in clinical trials, the extent of which is uncertain but may be large (Moore 2012b). Taken together with uncertainties about outcomes, the results we have were of low quality and made application of the evidence difficult.

The included studies were not designed, or of sufficient duration, to report on misuse or abuse of oxycodone in the long term.

Quality of the evidence

We downgraded the quality of the evidence to very low for all outcomes because of potential bias from imputation or completer analysis, heterogeneity in participant pain condition and study methods, and limited numbers of studies, participants, and events.

While all the included studies were randomised and double-blind, there were insufficient data to meet predefined criteria for first or second tier analysis for any outcomes. Most of the studies were small (the largest treatment group consisted of 165 participants) and, in particular, there were very few data from participants with PHN. Three of the studies were of short duration (treatment periods of four and six weeks) and two were of cross-over design without separate reporting of first period data. Two studies used LOCF imputation for withdrawals, two reported efficacy only for participants completing both phases of a cross-over, and the other study did not describe how missing data were analysed.

Potential biases in the review process

The absence of publication bias (unpublished trials showing no benefit of oxycodone over placebo) can never be proved. We carried out a broad search of studies and feel it is unlikely that significant amounts of relevant data remain unknown to us. We calculated that there would need to be additional data from 227 participants in studies demonstrating no effect to change the NNT to 10 for moderate benefit, a value at which we consider the treatment has little or no clinical benefit (Moore 2008).

The degree of exaggeration of treatment effects in cross-over trials compared to parallel group designs, as has been seen in some circumstances (Khan 1996), is unclear but is unlikely to be a source of major bias (Elbourne 2002). The two cross-over studies reported efficacy results only for those who completed both treatment periods, which is likely to overestimate efficacy, although we were able to calculate ITT data for the study contributing to 'moderate benefit'.

We chose to combine, for exploratory purposes, studies in two different pain conditions that used oxycodone alone or in combination with naloxone, as monotherapy or as an add-on therapy to inadequate treatment with an antiepileptic drug, and that used an inert placebo or 'active' placebo. Any of these 'differences' may influence the results of pooled analyses. As far as we could tell from subgroup analyses these effects were not substantial, but the amount of data available was too small to reliably show this.

Agreements and disagreements with other studies or reviews

The results of this review are in broad agreement with the relevant sections of European and UK guidelines on the use of oxycodone in the management of neuropathic pain (Attal 2010; NICE 2013). A review of all pharmacotherapy for neuropathic pain in adults found weak evidence for benefit of oxycodone in neuropathic pain conditions and recommended only third-line use due to safety concerns, particularly with long-term use (Finnerup 2015). Two wider reviews on the use of opioids for neuropathic pain identified the same three studies of oxycodone as monotherapy that are in this review, but carried out no separate analyses for individual opioids (McNicol 2013; Sommer 2015).

Other analyses of oxycodone in chronic pain have found no beneficial effect except where LOCF imputation was used and where adverse event withdrawals were high (Lange 2010). An RCT that added low dose (10 mg/day) oxycodone to pregabalin did not report enhanced analgesic efficacy (Zin 2010).

Evidence that used current best standards relevant to clinical effectiveness did not suggest a benefit of opioids over placebo for the treatment of chronic neuropathic pain (Moore 2012b), and an analysis of a large number of participants in trials of osteoarthritis and back pain showed oxycodone to be ineffective (Lange 2010).

AUTHORS' CONCLUSIONS

Implications for practice

Clinical trial evidence on the use of oxycodone in neuropathic pain conditions was limited to five studies in painful diabetic neuropathy and postherpetic neuralgia, all of which we considered at substantial risk of bias and likely to overestimate efficacy.

For people with neuropathic pain

There was very limited evidence that oxycodone (as oxycodone modified-release (MR)) may provide moderate benefit (equivalent to a 30% reduction in pain) to people with painful diabetic neuropathy or postherpetic neuralgia. There was no evidence for other neuropathic pain conditions. As with other opioids, some adverse events (particularly somnolence or sedation, constipation, and nausea) may limit its clinical usefulness.

For clinicians

There was very limited evidence that oxycodone (as oxycodone MR) may provide moderate benefit (equivalent to a 30% reduction in pain) to people with painful diabetic neuropathy or postherpetic neuralgia. There was no evidence for other neuropathic pain conditions. As with other opioids, some adverse events (particularly somnolence or sedation, constipation, and nausea) may limit its clinical usefulness. It might be expected that, at best, a few people with neuropathic pain will benefit from long-term use of oxycodone.

For policy makers

There was very limited evidence that oxycodone (as oxycodone MR) may provide moderate benefit (equivalent to a 30% reduction in pain) to people with painful diabetic neuropathy or postherpetic neuralgia. Common opioid adverse events may limit its clinical usefulness. There was no evidence for other neuropathic pain conditions. In the absence of high quality evidence of benefit, it should probably be used only at the discretion of a pain specialist with particular expertise in opioid use, and not as a first line treatment.

For funders

There was very limited evidence that oxycodone (as oxycodone MR) may provide moderate benefit (equivalent to a 30% reduction in pain) to people with painful diabetic neuropathy or postherpetic neuralgia. Common opioid adverse events may limit its clinical usefulness. There was no evidence for other neuropathic pain conditions. In the absence of high quality evidence of benefit, it should probably be used only at the discretion of a pain specialist

with particular expertise in opioid use, and not as a first line treatment.

Implications for research

General

For people with chronic neuropathic pain of moderate or severe intensity, treatment with oxycodone is likely to be more effective than placebo in only a small minority of cases. There may be differences in effect in different types of neuropathic pain. In this circumstance, to be certain of a result in terms of both direction and magnitude of effect would require very large clinical trials. These trials would need to have important design features.

- Be of long duration - a minimum of three months and perhaps longer.
- Use clear outcomes of clinical utility, approximating moderate and substantial benefit using several scoring systems, probably visual analogue scale (VAS) pain intensity and Patient Global Impression of Change scale (PGIC).
- Not use any imputation method, as the outcome desired is that of adequate pain relief in the longer term, and for that people have to continue on therapy. Withdrawal for any reason is treatment failure.
- Be clear from the beginning that treating people with opioid who do not have pain relief is unacceptable, so that there would be built-in stopping rules linked to pain relief after an adequate trial of therapy.
- Be designed and analysed to assess whether there are any predisposing features linked with treatment success or failure, and to determine stopping rules for adequate trial of therapy.

It may be that a more appropriate trial would be have an enriched enrolment randomised withdrawal design (Moore 2015). Discussion of a study with that design is outside the scope of this review.

Design

Trial designs may need to be radically different to capture answers to the research questions, but the key question is whether there are any people with neuropathic pain who do well on oxycodone in the long term; that is with a substantial reduction in pain maintained, and tolerable adverse events. An alternative to clinical trials might be the use of registry studies in non-cancer pain; preliminary suggestions for such a study have been published (Kim 2013).

Measurement (endpoints)

A major issue is not in the measurement of pain, as most studies, especially modern ones, have used standard pain intensity and pain relief scales. However, reporting of average pain changes is inadequate, and the use of responder analyses (at least 50% pain intensity reduction, or participants experiencing mild or no pain) is preferred. Long-term studies should aim to capture data on misuse and abuse of oxycodone.

Comparison between active treatments

Indirect comparisons with carrier are probably as informative as use of an active comparator.

ACKNOWLEDGEMENTS

This review was based on a template protocol developed in collaboration with the Cochrane Neuromuscular Diseases and Musculoskeletal Review Groups. The editorial process was managed by the Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS).

The Oxford Pain Relief Trust provided institutional support.

The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS). The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, National Health Service (NHS), or the Department of Health.

REFERENCES

References to studies included in this review

Gimbel 2003 *{published data only}*

* Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. *Neurology* 2003;**60**(6):927-34. [DOI: 10.1212/01.WNL.0000057720.36503.2C]

Jensen MP, Friedman M, Bonzo D, Richards P. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. *Pain* 2003;**105**(1-2):71-8. [DOI: 10.1016/S0304-3959(03)00160-X]

Hanna 2008 *{published data only}*

Hanna M, O'Brien C, Wilson MC. Prolonged-release oxycodone enhances the effects of existing gabapentin therapy in painful diabetic neuropathy patients. *European Journal of Pain* 2008;**12**(6):804-13. [DOI: 10.1016/j.ejpain.2007.12.010]

NCT00944697 *{unpublished data only}*

Mundipharma Research GmbH & Co KG (Responsible Party). An exploratory, randomised, double-blind, single-dummy, placebo controlled, parallel group study to demonstrate the analgesic efficacy of oxycodone/naloxone prolonged release tablets in addition to pregabalin compared to pregabalin alone in opioid-naïve subjects treated with pregabalin suffering from moderate to severe pain due to diabetic polyneuropathy, 2012. www.clinicaltrials.gov/ct2/show/NCT00944697 (accessed 4 February 2016). [CTG: NCT00944697]

Watson 1998 *{published data only}*

Watson CP, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. *Neurology* 1998;**50**(6):1837-41. [DOI: 10.1212/WNL.50.6.1837]

Watson 2003 *{published data only}*

Watson CP, Moulin D, Watt-Watson J, Gordon A, Eisenhoffer J. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. *Pain* 2003;**105**(1-2):71-8. [DOI: 10.1016/S0304-3959(03)00160-X]

References to studies excluded from this review

Buynak 2010 *{published data only}*

Buynak R, Shapiro DY, Okamoto A, Van Hove I, Rauschkolb C, Steup A, et al. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled Phase III study. *Expert Opinion on Pharmacotherapy* 2010;**11**(11):1787-804. [DOI: 10.1517/14656566.2010.497720]

EUCTR2004-003752-19-HU *{unpublished data only}*

EUCTR2004-003752-19-HU. A randomized, double-blind, placebo- and active-controlled, double-dummy, parallel group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in subjects with moderate to severe, chronic nonmalignant pain - OXN in moderate to severe, chronic nonmalignant pain, 2016. www.clinicaltrialsregister.eu/ctr-search/search?query=EUCTR2004-003752-19-HU (accessed 28 January 2016). [EUCTR2004-003752-19-HU]

EUCTR2005-003510-15-DE *{unpublished data only}*

EUCTR2005-003510-15-DE. A randomised, double-blind, double-dummy, parallel-group multicenter study to demonstrate improvement in symptoms of constipation in subjects with non-malignant pain taking oxycodone equivalent of 60 - 80 mg/day as oxycodone/naloxone prolonged release (OXN) compared to subjects taking oxycodone prolonged release tablets alone, 2016. www.clinicaltrialsregister.eu/ctr-search/search?query=EUCTR2005-003510-15-DE (accessed 28 January 2016). [EUCTR2005-003510-15-DE]

Gatti 2009 *{published data only}*

Gatti A, Sabato AF, Occhioni R, Colini Baldeschi G, Reale C. Controlled-release oxycodone and pregabalin in the treatment of neuropathic pain: results of a multicenter Italian study. *European Neurology* 2009;**61**(3):129-37. [DOI: 10.1159/000186502]

Green 2014 *{published and unpublished data}*

Green J, Dain B, Munera C, Gimbel J, Potts J, Berger B. A randomized, double-blind, placebo-controlled, multicenter trial to assess the efficacy and safety of oxycodone/ naloxone extended-release tablets (OXN) in opioid-experienced subjects with chronic low back pain. *Journal of Pain* 2014;**15**(4 Suppl 1):S89.

Purdue Pharma LP (Responsible Party). A randomized, double-blind, placebo-controlled, multicenter trial with an enriched study design to assess the efficacy and safety of oxycodone/ naloxone controlled-release tablets (oxn) compared to placebo in opioid-experienced subjects with moderate to severe pain due to chronic low back pain who require around-the-clock opioid therapy, 2015. www.clinicaltrials.gov/ct2/show/NCT01358526 (accessed 28 January 2016). [CliniclaTrials.gov: NCT01358526]

Hale 1999 *{published data only}*

Hale ME, Fleischmann R, Salzman R, Wild J, Iwan T, Swanton RE, et al. Efficacy and safety of controlled-release versus immediate-release oxycodone: randomized, double-blind evaluation in patients with chronic back pain. *Clinical Journal of Pain* 1999;**15**(3):179-83. [PUBMED: 10524470]

Hale 2005 *{published data only}*

Hale ME, Dvergsten C, Gimbel J. Efficacy and safety of oxymorphone extended release in chronic low back pain: results of a randomized, double-blind, placebo- and active-controlled phase III study. *Journal of Pain* 2005;**6**(1):21-8. [DOI: 10.1016/j.jpain.2004.09.005]

He 2009 *{published data only}*

He B-Y. Analgesic effect of oxycodone-acetaminophen tablet in treatment of backleg pain [*sic*]. *Chinese Journal of New Drugs* 2009;**18**(7):623-5. [EMBASE: 2009220662]

ISRCTN76170309 *{unpublished data only}*

ISRCTN76170309. A randomised, crossover study of study drug 038 and controlled-release oxycodone HCl tablets in patients with chronic non-cancer pain, 2016. www.isrctn.com/ISRCTN76170309 (accessed 28 January 2016). [DOI: 10.1186/ISRCTN76170309]

Kopecky 2015 *{published and unpublished data}*

* Kopecky E, O'Connor M, Varanasi R, Saim S, Fleming A. Efficacy and safety of oxycodone DETERx: results of a randomized, double-blind, placebo-controlled phase III study. *Journal of Pain* 2015;**16**(4):S87. [DOI: 10.1016/j.jpain.2015.01.364]

Kopecky EA (Study director). A phase 3, multi-center, randomized, double-blind, placebo-controlled, safety, tolerability, and efficacy study of oxycodone DETERx™ versus placebo in opioid-experienced and opioid-naive subjects with moderate-to-severe chronic low back pain, 2016. www.clinicaltrials.gov/ct2/show/NCT01685684 (accessed 28 January 2016). [CTG: NCT01685684]

Lange 2010 *{published data only}*

Lange B, Kuperwasser B, Okamoto A, Steup A, Häufel T, Ashworth J, et al. Efficacy and safety of tapentadol prolonged release for chronic osteoarthritis pain and low back pain. *Advances in Therapy* 2010;**27**(6):381-99. [DOI: 10.1007/s12325-010-0036-3]

Löwenstein 2009 *{published and unpublished data}*

* Löwenstein O, Leyendecker P, Hopp M, Schutter U, Rogers PD, Uhl R, et al. Combined prolonged-release oxycodone and naloxone improves bowel function in patients receiving opioids for moderate-to-severe non-malignant chronic pain: a randomised controlled trial. *Expert Opinion on Pharmacotherapy* 2009;**10**(4):531-43. [DOI: 10.1517/14656560902796798]

NCT00412100. A randomised [sic], double-blind, double-dummy, parallel-group multicentre study to demonstrate improvement in symptoms of constipation in subjects with non-malignant pain taking oxycodone equivalent of 60-80 mg/day as oxycodone/naloxone prolonged release compared to subjects taking oxycodone prolonged release tablets alone, 2016. www.clinicaltrials.gov/ct2/show/NCT00412100 (accessed 28 January 2016). [ClinicalTrials.gov : NCT00412100]

NCT00414453 *{unpublished data only}*

Dworkin RH (Principal investigator). Trial of analgesia with lidocaine or extended-release oxycodone for neuropathic pain treatment in multiple sclerosis (TALENT-MS), 2016. www.clinicaltrials.gov/ct2/show/NCT00414453 (accessed 28 January 2016). [CTG: NCT00414453]

NCT00449176 *{unpublished data only}*

NCT0049176. A study to evaluate the effectiveness and safety of tapentadol (CG5503) extended release (ER) in patients with moderate to severe chronic low back pain, 2016. www.clinicaltrials.gov/ct2/show/NCT0049176 (accessed 28 January 2016). [CTG: NCT0049176]

NCT00784810 *{unpublished data only}*

NCT00784810. A double-blind, double-dummy, parallel group, randomised study to compare the efficacy & tolerability of oxycodone/naloxone prolonged release (OXN PR) & codeine/paracetamol in the treatment of moderate to severe chronic low back pain or pain due to osteoarthritis, 2016. www.clinicaltrials.gov/ct2/show/NCT00784810 (accessed 28 January 2016). [CTG: NCT00784810]

NCT01014559 *{unpublished data only}*

NCT01014559. Study of efficacy of OXN PR, compared to Oxy PR, for reduction of intensity of opioid-induced constipation symptoms in pts treated for cancer or non-cancer pain: a randomised, double-blind, controlled, multicentre study, 2016. www.clinicaltrials.gov/ct2/show/NCT01014559 (accessed 28 January 2016). [CTG: NCT01014559]

NCT01427270 *{unpublished data only}*

NCT01427270. A randomized, double-blind, double-dummy, placebo-controlled, active-controlled, parallel-group, multicenter trial of oxycodone/naloxone controlled-release tablets (OXN) to assess the analgesic efficacy (compared to placebo) and the management of opioid-induced constipation (compared to oxycodone controlled-release tablets (OXY)) in opioid-experienced subjects with uncontrolled moderate to severe chronic low back pain and a history of opioid-induced constipation who require around-the-clock opioid therapy, 2016. www.clinicaltrials.gov/ct2/show/NCT01427270 (accessed 28 January 2016). [CTG: NCT01427270]

NCT01427283 *{unpublished data only}*

NCT01427283. A randomized, double-blind, double-dummy, placebo-controlled, active-controlled, parallel-group, multicenter trial of oxycodone/naloxone controlled-release tablets (OXN) to assess the analgesic efficacy (compared to placebo) and the management of opioid-induced constipation (compared to oxycodone controlled-release tablets (OXY)) in opioid-experienced subjects with moderate to severe chronic low back pain and a history of opioid-induced constipation who require around-the-clock opioid therapy, 2016. www.clinicaltrials.gov/ct2/show/NCT01427283 (accessed 28 January 2016). [CTG: NCT01427283]

NCT01438567 *{unpublished data only}*

NCT01438567. A randomised, double-blind, double-dummy, parallel-group multicenter study to demonstrate improvement in symptoms of constipation and non-inferiority in analgesic efficacy in subjects with non-malignant or malignant pain that require around-the-clock opioid therapy taking 50/25 - 80/40 mg twice daily as oxycodone/naloxone prolonged release (OXN PR) tablets compared to subjects taking 50 - 80 mg twice daily oxycodone prolonged release (OxyPR) tablets alone, 2016. www.clinicaltrials.gov/ct2/show/NCT01438567 (accessed 28 January 2016). [CTG: NCT01438567]

NCT01439100 *{unpublished data only}*

NCT01439100. A randomised placebo controlled study of OXN PR for severe Parkinson's disease associated pain, 2016. www.clinicaltrials.gov/ct2/show/NCT01439100 (accessed 28 January 2016). [CTG: NCT01439100]

NCT01502644 *{unpublished data only}*

NCT01502644. Opioid treatment for chronic low back pain and the impact of mood symptoms, 2016. www.clinicaltrials.gov/ct2/show/NCT01502644 (accessed 28 January 2016). [CTG: NCT01502644]

NCT02321397 *{unpublished data only}*

NCT02321397. Randomised, double-blind, double-dummy, cross-over multicenter study to demonstrate equivalence in analgesic efficacy & bowel function taking oxycodone equivalents of 120 & 160 mg per day as achieved with the higher OXN PR tablet strengths (OXN60/30 mg PR, OXN80/40 mg PR) BID compared to the identical daily dose taken as a combination of lower tablet strengths in subjects with non-malignant or malignant pain that requires around-the-clock opioid therapy, 2016. www.clinicaltrials.gov/ct2/show/NCT02321397 (accessed 28 January 2016). [CTG: NCT02321397]

Simpson 2008 *{published and unpublished data}*

Simpson K (Principal investigator). A randomised, double-blind, parallel-group, multicentre study to demonstrate improvement in symptoms of constipation in subjects with non-malignant pain taking oxycodone equivalent of >20 mg/day and <50 mg/day as oxycodone/naloxone prolonged release compared to subjects taking oxycodone prolonged release tablets alone, 2016. www.clinicaltrials.gov/ct2/show/NCT00412152 (accessed 28 January 2016). [CTG: NCT00412152]

* Simpson K, Leyendecker P, Hopp M, Müller-Lissner S, Löwenstein O, De Andrés J, et al. Fixed-ratio combination oxycodone/naloxone compared with oxycodone alone for the relief of opioid-induced constipation in moderate-to-severe noncancer pain. *Current Medical Research and Opinion* 2008;**24**(12):3503-12. [DOI: 10.1185/03007990802584454]

Steiner 2011 *{published and unpublished data}*

NCT00313014. A multicenter, randomized, double-blind, active comparator study to determine the efficacy and safety of BTDS 20 or oxycodone immediate-release versus BTDS 5 in subjects with moderate to severe low back pain, 2016. www.clinicaltrials.gov/ct2/show/NCT00313014 (accessed 28 January 2016). [CTG: NCT00313014]

Steiner D, Munera C, Hale M, Ripa S, Landau C. Efficacy and safety of buprenorphine transdermal system (BTDS) for chronic moderate to severe low back pain: a randomized, double-blind study. *Journal of Pain* 2011;**12**(11):1163-73. [DOI: 10.1016/j.jpain.2011.06.003]

Vondrackova 2008 *{published and unpublished data}*

NCT01971632. A randomised, double blind, placebo and active controlled, double dummy, parallel group study to determine the safety and efficacy of oxycodone/naloxone prolonged release tablets in subjects with moderate to severe, chronic nonmalignant pain, 2016. www.clinicaltrials.gov/ct2/show/NCT01971632 (accessed 28 January 2016). [CTG: NCT01971632]

* Vondrackova D, Leyendecker P, Meissner W, Hopp M, Szombati I, Hermanns K, et al. Analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release tablets in patients with moderate to severe chronic pain. *Journal of Pain* 2008;**9**(12):1144-54. [DOI: 10.1016/j.jpain.2008.06.014]

Webster 2006 *{published data only}*

Webster LR, Butera PG, Moran LV, Wu N, Burns LH, Friedmann N. Oxytrex minimizes physical dependence while providing effective analgesia: a randomized controlled trial in low back pain. *Journal of Pain* 2006;**7**(12):937-46. [DOI: 10.1016/j.jpain.2006.05.005]

Wild 2010 *{published data only}*

Wild JE, Grond S, Kuperwasser B, Gilbert J, McCann B, Lange B, et al. Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. *Pain Practice* 2010;**10**(5):416-27. [DOI: 10.1111/j.1533-2500.2010.00397.x]

Wörz 2003 *{published data only}*

Wörz R, Frank M, Achenbach U. Controlled-release oxycodone - a therapeutic option for severe neuropathic pain. *MMW Fortschritte der Medizin* 2003;**145**(39):45. [PUBMED: 15490770]

Zin 2010 *{published data only}*

Zin CS, Nissen LM, O'Callaghan JP, Duffull SB, Smith MT, Moore BJ. A randomized, controlled trial of oxycodone versus placebo in patients with postherpetic neuralgia and painful diabetic neuropathy treated with pregabalin. *Journal of Pain* 2010;**11**(5):462-71. [DOI: 10.1016/j.jpain.2009.09.003.]

Additional references

Attal 2010

Attal N, Cruccu G, Baron R, Haanpää M, Hansson P, Jensen TS, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *European Journal of Neurology* 2010;**17**(9):1113-e88. [DOI: 10.1111/j.1468-1331.2010.02999.x]

Ballantyne 2016

Ballantyne JC, Kalso E, Stannard C. WHO analgesic ladder: a good concept gone astray. *BMJ* 2016;**352**:i20. [DOI: 10.1136/bmj.i20]

Baron 2012

Baron R, Wasner G, Binder A. Chronic pain: genes, plasticity, and phenotypes. *Lancet Neurology* 2012;**11**(1):19-21. [DOI: 10.1016/S1474-4422(11)70281-2]

Bostick 2015

Bostick GP, Toth C, Carr EC, Stitt LW, Morley-Forster P, Clark AJ, et al. Physical functioning and opioid use in patients with neuropathic pain. *Pan Medicine* 2015;**6**(7):1361-8. [DOI: 10.1111/pme.12702]

Bouhassira 2008

Bouhassira D, Lantéri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. *Pain* 2008;**136**(3):380-7. [DOI: 10.1016/j.pain.2007.08.013]

Brennan 2013

Brennan MJ. The effect of opioid therapy on endocrine function. *American Journal of Medicine* 2013;**126**(3 Suppl 1):S12-8. [DOI: 10.1016/j.amjmed.2012.12.001]

Butler 2013

Butler SF, Cassidy TA, Chilcoat H, Black RA, Landau C, Budman SH, et al. Abuse rates and routes of administration of reformulated extended-release oxycodone: initial findings from a sentinel surveillance sample of individuals assessed for substance abuse treatment. *Journal of Pain* 2013;**14**(4):351-8. [DOI: 10.1016/j.jpain.2012.08.008]

Calvo 2012

Calvo M, Dawes JM, Bennett DL. The role of the immune system in the generation of neuropathic pain. *Lancet Neurology* 2012;**11**(7):629-42. [DOI: 10.1016/S1474-4422(12)70134-5]

Dechartres 2013

Dechartres A, Trinquart L, Boutron I, Ravaud P. Influence of trial sample size on treatment effect estimates: meta-epidemiological study. *BMJ* 2013;**346**:f2304. [DOI: 10.1136/bmj.f2304]

Demant 2014

Demant DT, Lund K, Vollert J, Maier C, Segerdahl M, Finnerup NB, et al. The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: a randomised, double-blind, placebo-controlled phenotype-stratified study. *Pain* 2014;**155**(11):2263-73. [DOI: 10.1016/j.pain.2014.08.014]

Derry 2012

Derry S, Moore RA. Topical capsaicin (low concentration) for chronic neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 9. [DOI: 10.1002/14651858.CD010111]

Derry 2013

Derry S, Sven-Rice A, Cole P, Tan T, Moore RA. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 2013, Issue 2. [DOI: 10.1002/14651858.CD007393.pub3]

Derry 2014

Derry S, Wiffen PJ, Moore RA, Quinlan J. Topical lidocaine for neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 2014, Issue 7. [DOI: 10.1002/14651858.CD010958.pub2]

Dhalla 2009

Dhalla IA, Mamdani MM, Sivilotti ML, Kopp A, Qureshi O, Juurlink DN. Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. *Canadian Medical Association Journal* 2009;**181**(12):891-6. [DOI: 10.1503/cmaj.090784]

Dworkin 2007

Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* 2007;**132**(3):237-51. [DOI: 10.1016/j.pain.2007.08.033]

Dworkin 2008

Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *Journal of Pain* 2008;**9**(2):105-21. [DOI: 10.1016/j.jpain.2007.09.005]

Elbourne 2002

Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140-9. [DOI: 10.1093/ije/31.1.140]

Finnerup 2013

Finnerup NB, Scholz J, Attal N, Baron R, Haanpää M, Hansson P, et al. Neuropathic pain needs systematic classification. *European Journal of Pain* 2013;**17**(7):953-6. [DOI: 10.1002/j.1532-2149.2012.00282.x]

Finnerup 2015

Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurology* 2015;**14**(2):162-73. [DOI: 10.1016/S1474-4422(14)70251-0]

Gaskell 2009

Gaskell H, Derry S, Moore RA, McQuay HJ. Single dose oral oxycodone and oxycodone plus paracetamol (acetaminophen) for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD002763.pub2]

GRADEpro GDT 2016 [Computer program]

McMaster University (developed by Evidence Prime, Inc.). GRADEpro Guideline Development Tool [Software]. Available from www.gradepro.org (accessed 3 March 2016). McMaster University (developed by Evidence Prime, Inc.), 2016.

Gustorff 2008

Gustorff B, Dorner T, Likar R, Grisold W, Lawrence K, Schwarz F, et al. Prevalence of self-reported neuropathic pain and impact on quality of life: a prospective representative survey. *Acta Anaesthesiologica Scandinavica* 2008;**52**(1):132-6. [DOI: 10.1111/j.1399-6576.2007.01486.x]

Guyatt 2013a

Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. *Journal of Clinical Epidemiology* 2013;**66**(2):151-7. [DOI: 10.1016/j.jclinepi.2012.01.006]

Guyatt 2013b

Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. *Journal of Clinical Epidemiology* 2013;**66**(2):158-72. [DOI: 10.1016/j.jclinepi.2012.01.012]

Hall 2008

Hall GC, Carroll D, McQuay HJ. Primary care incidence and treatment of four neuropathic pain conditions: a descriptive

study, 2002-2005. *BMC Family Practice* 2008;**9**:26. [DOI: 10.1186/1471-2296-9-26]

Hall 2013

Hall GC, Morant SV, Carroll D, Gabriel ZL, McQuay HJ. An observational descriptive study of the epidemiology and treatment of neuropathic pain in a UK general population. *BMC Family Practice* 2013;**14**:28. [DOI: 10.1186/1471-2296-14-28]

Helfert 2015

Helfert SM, Reimer M, Höper J, Baron R. Individualized pharmacological treatment of neuropathic pain. *Clinical Pharmacology and Therapeutics* 2015;**97**(2):135-42. [DOI: 10.1002/cpt.19]

Higgins 2011a

Higgins JPT, Altman DG, Sterne JAC. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [update March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011b

Higgins JPT, Altman DG, Sterne JAC. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hoffman 2010

Hoffman DL, Sadosky A, Dukes EM, Alvir J. How do changes in pain severity levels correspond to changes in health status and function in patients with painful diabetic peripheral neuropathy?. *Pain* 2010;**149**(2):194-201. [DOI: 10.1016/j.pain.2009.09.017]

Jadad 1996

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary?. *Controlled Clinical Trials* 1996;**17**(1):1-12. [DOI: 10.1016/0197-2456(95)00134-4]

Jensen 2011

Jensen TS, Baron R, Haanpää M, Kalso E, Loeser JD, Rice AS, et al. A new definition of neuropathic pain. Pain 2011; Vol. 152, issue 10:2204-5. [DOI: 10.1016/j.pain.2011.06.017]

Kalso 2007

Kalso E. How different is oxycodone from morphine?. *Pain* 2007;**132**(3):227-8. [DOI: 10.1016/j.pain.2007.09.027]

Kalso 2013

Kalso E, Aldington DJ, Moore RA. Drugs for neuropathic pain. *BMJ* 2013;**347**:f7339. [DOI: 10.1136/bmj.f7339]

Katusic 1991

Katusic S, Williams DB, Beard CM, Bergstralh EJ, Kurland LT. Epidemiology and clinical features of idiopathic trigeminal neuralgia and glossopharyngeal neuralgia: similarities and differences, Rochester, Minnesota, 1945-1984. *Neuroepidemiology* 1991;**10**:276-81. [PUBMED: 1798430]

Khan 1996

Khan KS, Daya S, Jadad A. The importance of quality of primary studies in producing unbiased systematic reviews. *Archives of Internal Medicine* 1996;**156**(6):661-6. [DOI: 10.1001/archinte.1996.00440060089011]

Kim 2013

Kim M, Chow W, Benson C. Rationale and design of the Oxycodone Users Registry: a prospective, multicenter registry of patients with nonmalignant pain. *Journal of Opioid Management* 2013;**9**(3):189-204. [DOI: 10.5055/jom.2013.0160]

Koopman 2009

Koopman JS, Dieleman JP, Huygen FJ, de Mos M, Martin CG, Sturkenboom MC. Incidence of facial pain in the general population. *Pain* 2009;**147**(1-3):122-7. [DOI: 10.1016/j.pain.2009.08.023]

L'Abbé 1987

L'Abbé KA, Detsky AS, O'Rourke K. Meta-analysis in clinical research. *Annals of Internal Medicine* 1987;**107**:224-33. [DOI: 10.7326/0003-4819-107-2-224]

Lunn 2014

Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. *Cochrane Database of Systematic Reviews* 2014, Issue 1. [DOI: 10.1002/14651858.CD007115.pub3]

McNicol 2013

McNicol ED, Midbari A, Eisenberg E. Opioids for neuropathic pain. *Cochrane Database of Systematic Reviews* 2013, Issue 8. [DOI: 10.1002/14651858.CD006146.pub2]

McQuay 1998

McQuay H, Moore R. An Evidence-Based Resource for Pain Relief. Oxford: Oxford University Press, 1998. [ISBN: 0-19-263048-2]

Moore 1998

Moore RA, Gavaghan D, Tramèr MR, Collins SL, McQuay HJ. Size is everything - large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. *Pain* 1998;**78**(3):209-16. [DOI: 10.1016/S0304-3959(98)00140-7]

Moore 2008

Moore RA, Barden J, Derry S, McQuay HJ. Managing potential publication bias. In: McQuay HJ, Kalso E, Moore RA editor(s). Systematic Reviews in Pain Research: Methodology Refined. Seattle: IASP Press, 2008:15-24. [ISBN: 978-0-931092-69-5]

Moore 2009

Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD007076.pub2]

Moore 2010a

Moore RA, Eccleston C, Derry S, Wiffen P, Bell RF, Straube S, et al. "Evidence" in chronic pain - establishing best practice in the reporting of systematic reviews. *Pain* 2010;**150**(3):386-9. [DOI: 10.1016/j.pain.2010.05.011]

Moore 2010b

Moore RA, Straube S, Derry S, McQuay HJ. Chronic low back pain analgesic studies - a methodological minefield. *Pain* 2010;**149**(3):431-4. [DOI: 10.1016/j.pain.2010.02.032]

Moore 2010c

Moore RA, Moore OA, Derry S, Peloso PM, Gammaitoni AR, Wang H. Responder analysis for pain relief and numbers needed to treat in a meta-analysis of etoricoxib osteoarthritis trials: bridging a gap between clinical trials and clinical practice. *Annals of the Rheumatic Diseases* 2010;**69**(2):374-9. [DOI: 10.1136/ard.2009.107805]

Moore 2010d

Moore RA, Straube S, Paine J, Phillips CJ, Derry S, McQuay HJ. Fibromyalgia: moderate and substantial pain intensity reduction predicts improvement in other outcomes and substantial quality of life gain. *Pain* 2010;**149**(2):360-4. [DOI: 10.1016/j.pain.2010.02.039]

Moore 2010e

Moore RA, Smugar SS, Wang H, Peloso PM, Gammaitoni A. Numbers-needed-to-treat analyses - do timing, dropouts, and outcome matter? Pooled analysis of two randomized, placebo-controlled chronic low back pain trials. *Pain* 2010;**151**(3):592-7. [DOI: 10.1016/j.pain.2010.07.013]

Moore 2011a

Moore RA, Straube S, Paine J, Derry S, McQuay HJ. Minimum efficacy criteria for comparisons between treatments using individual patient meta-analysis of acute pain trials: examples of etoricoxib, paracetamol, ibuprofen, and ibuprofen/paracetamol combinations after third molar extraction. *Pain* 2011;**152**(5):982-9. [DOI: 10.1016/j.pain.2010.11.030]

Moore 2011b

Moore RA, Mhuircheartaigh RJ, Derry S, McQuay HJ. Mean analgesic consumption is inappropriate for testing analgesic efficacy in post-operative pain: analysis and alternative suggestion. *European Journal of Anaesthesiology* 2011;**28**(6):427-32. [DOI: 10.1097/EJA.0b013e328343c569]

Moore 2012a

Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for neuropathic pain and fibromyalgia in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 12. [DOI: 10.1002/14651858.CD008242.pub2]

Moore 2012b

Moore RA, Straube S, Eccleston C, Derry S, Aldington D, Wiffen P, et al. Estimate at your peril: imputation methods for patient withdrawal can bias efficacy outcomes in chronic pain trials using responder analyses. *Pain* 2012;**153**(2):265-8. [DOI: 10.1016/j.pain.2011.10.004]

Moore 2013a

Moore RA, Straube S, Aldington D. Pain measures and cut-offs — 'no worse than mild pain' as a simple, universal outcome. *Anaesthesia* 2013;**68**(4):400-12. [DOI: 10.1111/anae.12148]

Moore 2013b

Moore A, Derry S, Eccleston C, Kalso E. Expect analgesic failure; pursue analgesic success. *BMJ* 2013;**346**:f2690. [DOI: 10.1136/bmj.f2690]

Moore 2014a

Moore RA, Derry S, Taylor RS, Straube S, Phillips CJ. The costs and consequences of adequately managed chronic non-cancer pain and chronic neuropathic pain. *Pain Practice* 2014;**14**(1):79-94. [DOI: 10.1111/papr.12050]

Moore 2014b

Moore RA, Derry S, Taylor RS, Straube S, Phillips CJ. The costs and consequences of adequately managed chronic non-cancer pain and chronic neuropathic pain. *Pain Practice* 2014;**14**(1):79-94. [DOI: 10.1111/papr.12050]

Moore 2014c

Moore RA, Wiffen PJ, Derry S, McQuay HJ. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database of Systematic Reviews* 2014, Issue 4. [DOI: 10.1002/14651858.CD007938.pub3]

Moore 2014d

Moore RA, Cai N, Skljarevski V, Tölle TR. Duloxetine use in chronic painful conditions - individual patient data responder analysis. *European Journal of Pain* 2014;**18**(1):67-75. [DOI: 10.1002/j.1532-2149.2013.00341.x]

Moore 2015

Moore RA, Wiffen PJ, Eccleston C, Derry S, Baron R, Bell RF, et al. Systematic review of enriched enrolment, randomised withdrawal trial designs in chronic pain: a new framework for design and reporting. *Pain* 2015;**156**(8):1382-95. [DOI: 10.1097/j.pain.0000000000000088]

NICE 2013

National Institute for Health and Clinical Excellence. Neuropathic pain: the pharmacological management of neuropathic pain in adults in non-specialist settings, 2013. www.nice.org.uk/guidance/CG173 (accessed 26 January 2016).

Nüesch 2010

Nüesch E, Trelle S, Reichenbach S, Rutjes AW, Tschannen B, Altman DG, et al. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. *BMJ* 2010;**341**:c3515. [DOI: 10.1136/bmj.c3515]

O'Brien 2010

O'Brien EM, Staud RM, Hassinger AD, McCulloch RC, Craggs JG, Atchison JW, et al. Patient-centered perspective on treatment outcomes in chronic pain. *Pain Medicine* 2010;**11**(1):6-15. [DOI: 10.1111/j.1526-4637.2009.00685.x]

Olkkola 2009

Olkkola KT, Hagelberg NM. Oxycodone: new 'old' drug. *Current Opinions in Anaesthesiology* 2009;**22**(4):459-62. [DOI: 10.1097/ACO.0b013e32832bc818]

Olkkola 2013

Olkkola KT, Kontinen VK, Saari TI, Kalso EA. Does the pharmacology of oxycodone justify its increasing use as an analgesic?. *Trends in Pharmacological Sciences* 2013;**34**(4):206-14. [DOI: 10.1016/j.tips.2013.02.001]

PaPaS 2012

Cochrane Pain, Palliative and Supportive Care Group (PaPaS) author and referee guidance. papas.cochrane.org/papas-documents (accessed 26 January 2016).

Poyhia 1993

Poyhia R, Vainio A, Kalso E. A review of oxycodone's clinical pharmacokinetics and pharmacodynamics. *Journal of Pain & Symptom Management* 1993;**8**(2):63-7. [PUBMED: 8492004]

Rappaport 1994

Rappaport ZH, Devor M. Trigeminal neuralgia: the role of self-sustaining discharge in the trigeminal ganglion. *Pain* 1994;**56**:127-38. [DOI: 10.1016/0304-3959(94)90086-8]

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Schmidt-Hansen 2015

Schmidt-Hansen M, Bennett MI, Arnold S, Bromham N, Hilgart JS. Oxycodone for cancer-related pain. *Cochrane Database of Systematic Reviews* 2015, Issue 2. [DOI: 10.1002/14651858.CD003870.pub5]

Sommer 2015

Sommer C, Welsch P, Klose P, Schaefert R, Petzke F, Häuser W. Opioids in chronic neuropathic pain. A systematic review and meta-analysis of efficacy, tolerability and safety in randomized placebo-controlled studies of at least 4 weeks duration. *Schmerz* 2015;**29**(1):35-46. [DOI: 10.1007/s00482-014-1455-x]

Stannard 2013

Stannard C. Opioids in the UK: what's the problem?. *BMJ* 2013;**347**:f5108. [DOI: 10.1136/bmj.f5108]

Straube 2008

Straube S, Derry S, McQuay HJ, Moore RA. Enriched enrollment: definition and effects of enrichment and dose in trials of pregabalin and gabapentin in neuropathic pain. A systematic review. *British Journal of Clinical Pharmacology* 2008;**66**(2):266-75. [DOI: 10.1111/j.1365-2125.2008.03200.x]

Sultan 2008

Sultan A, Gaskell H, Derry S, Moore RA. Duloxetine for painful diabetic neuropathy and fibromyalgia pain: systematic review of randomised trials. *BMC Neurology* 2008;**8**:29. [DOI: 10.1186/1471-2377-8-29]

Torrance 2006

Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin: results from a general population survey. *Journal of Pain* 2006;**7**(4):281-9. [DOI: 10.1016/j.jpain.2005.11.008]

Treede 2008

Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology* 2008;**70**(18):1630-5. [DOI: 10.1212/01.wnl.0000282763.29778.59]

van Hecke 2014

van Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: a systematic review of epidemiological studies. *Pain* 2014;**155**(4):654-62. [DOI: 10.1016/j.pain.2013.11.013]

von Hehn 2012

von Hehn CA, Baron R, Woolf CJ. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. *Neuron* 2012;**73**(4):638-52. [DOI: 10.1016/j.neuron.2012.02.008]

Vos 2012

Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;**380**(9859):2163-96. [DOI: 10.1016/S0140-6736(12)61729-2]

Wiffen 2013

Wiffen PJ, Derry S, Moore RA, Aldington D, Cole P, Rice ASC, et al. Antiepileptic drugs for neuropathic pain and fibromyalgia - an overview of Cochrane reviews. *Cochrane Database of Systematic Reviews* 2013, Issue 11. [DOI: 10.1002/14651858.CD010567.pub2]

References to other published versions of this review

Gaskell 2014

Gaskell H, Moore RA, Derry S, Stannard C. Oxycodone for neuropathic pain and fibromyalgia in adults. *Cochrane Database of Systematic Reviews* 2014, Issue 6. [DOI: 10.1002/14651858.CD010692.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Gimbel 2003

Methods	Multicentre, randomised, double-blind, placebo-controlled parallel group study Study duration: screening and washout for 3 to 7 days followed by 42 day treatment phase
Participants	Diabetic with symmetrical, distal polyneuropathy Average PI ≥ 5/10 for ≥ 12 hours/day for ≥ 3 months, and ≥ moderate PI in absence of opioid therapy Diabetes stable, with HbA1c ≤ 11% Exclusions: significant co-morbidities (including impaired renal function), pain of other aetiology, opioid allergy or intolerance, history of drug or alcohol abuse, pregnancy or breastfeeding N = 159 Mean (± SD) age: 59 (± 11) years M 83, F 76 Mean (± SD) baseline PI 7/10 (± 1.4) Mean (± SD) baseline HbA1c 7.8 (± 1.4)
Interventions	All pre-study opioid drugs discontinued for ≥ 3 days before starting study medication. Other stable analgesics and diabetic medications continued unchanged Oxycodone MR to maximum 120 mg/day, n = 82 Placebo, n = 77 Starting dose 10 mg, twice daily. Dose titrated upwards by 10 mg twice daily every 3 days. Optional 1 week taper at end Mean (± SD) daily dose: Oxycodone 37 (± 21) mg Placebo 52 (± 25) mg Mean (± SD) daily dose in last 2 weeks for oxycodone 42 (± 27) mg Dose reduction allowed if adverse events intolerable. No opioid rescue medication allowed
Outcomes	Daily diary: • Average daily PI (0 to 10) in last 24 hours (days 28 to 42), NPS • Also scored for current pain, worst pain, satisfaction, sleep quality • BPI • Psychological state, physical functioning, mental health, SF-36 • Days with mild pain (PI ≤ 4/10) • Adverse events LOCF for withdrawal Intermittent missing data not imputed ITT: all participants randomised and receiving ≥ 1 dose study medication Responder analysis of NPS items (Gimbel 2003 in Jensen 2006)
Notes	Oxford Quality Score: R2, DB2, W1 Total = 5/5 Recruitment: not reported

Gimbel 2003 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated by sponsor centrally
Allocation concealment (selection bias)	Low risk	Remotely packaged and shipped to sites; "subject numbers assigned in ascending sequence as subjects qualified for randomisation"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Matching placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Matching placebo"
Incomplete outcome data (attrition bias) All outcomes	High risk	LOCF for withdrawal Intermittent missing data not imputed
Size	Unclear risk	Between 50 to 199 participants per treatment arm

Hanna 2008

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel group. Add-on design Study duration: 12 weeks
Participants	Painful diabetic neuropathy (≥ 3 months). Stable maximum tolerated dose of gabapentin (≥ 1 month), but PI ≥ 5/10. HbA1c ≤ 11% Exclusions: long-acting opioid in previous month or previous treatment with oxycodone + gabapentin N = 338 (randomised), 328 (efficacy), 335 (safety) M 210, F 118 Mean (± SD) age: 60 (± 10) years
Interventions	Oxycodone PR, n = 163 Placebo, n = 165 (full analysis population) Dose started at 5 mg daily, increased or decreased in stepwise manner as necessary All participants were treated with stable doses of gabapentin
Outcomes	Mean PI at end of study Use of rescue medication Adverse events

Hanna 2008 *(Continued)*

	Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1 Total = 5/5 Recruitment: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation schedule prepared by Mundipharma Clinical Supplies Department (review authors judged low risk)
Allocation concealment (selection bias)	Low risk	Remote, voice response system
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"matched placebo"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"matched placebo"
Incomplete outcome data (attrition bias) All outcomes	High risk	LOCF
Size	Unclear risk	50 to 199 participants per treatment arm

NCT00944697

Methods	Multicentre, randomised, placebo-controlled, double-blind, single-dummy, parallel group study. Add-on design Study duration: 12 weeks
Participants	Painful diabetic polyneuropathy (PI ≥ 5/10), opioid naive, aged ≥ 18 years Exclusions: impaired liver/kidney function, significant structural abnormality of the gastrointestinal tract, pregnancy or breastfeeding N = 98 M 50, F 48 Mean age (± SD): 61 (± 10) years
Interventions	Oxycodone PR + naloxone (dose not specified), n = 48 Placebo, n = 50 All participants were treated with stable doses of pregabalin
Outcomes	Group mean Short Form McGill Pain Score at 12 weeks Adverse events

NCT00944697 *(Continued)*

	Serious adverse events
	Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1 Total = 3/5
	Recruitment: primary, secondary, and tertiary care

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"single dummy" method
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"single dummy" method
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation not reported
Size	High risk	< 50 participants per treatment arm

Watson 1998

Methods	Single-centre, randomised, double-blind, placebo-controlled, two-way cross-over study medication
	Study duration: washout period ≥ 7 days, then treatment phase of 2 periods of 4 weeks, without washout at cross-over
Participants	Postherpetic neuralgia for ≥ 3 months, with pain of at least moderate intensity for at least half of the day
	Exclusions: pain of other aetiology, opioid allergy or intolerance, history of drug or alcohol abuse
	N = 50
	Mean (± SD) age: 70 (± 11) years
	M 16, F 22 (in efficacy analysis)
Interventions	All pre-study opioid drugs discontinued ≥ 7 days before starting study medication
	Other stable medications for pain (taken for ≥ 3 weeks) continued unchanged
	Oxycodone MR to maximum 60 mg/day, n = 50
	Placebo, n = 50

Watson 1998 *(Continued)*

	Starting dose 10 mg, twice daily. Dose titrated upwards at a maximum rate of 10 mg twice daily, at weekly visits over 4 weeks Mean (± SD) daily dose during final week 45 (± 17) mg
Outcomes	Diary: • Daily overall PI (100 mm VAS and 5-point categorical scale) • Daily overall pain relief (6-point categorical scale) • Intensity of steady, brief, and skin pain over previous week (100 mm VAS and 5-point categorical scale) Weekly (investigator rated following participant interview): • Disability (scale 0 to 3) • Effectiveness (scale 0 to 4) • Affective state (POMS, BDI) Adverse events assessed using "non-directed questionnaire" End of study: Treatment preference (assessed under double-blind conditions)
Notes	Oxford Quality Score: R1, DB2, W1 Total = 4/5 Recruitment: spontaneous referrals to chronic pain specialist and via newspaper advertising

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Assignment in opaque envelope, but not recorded if envelope sealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Matching placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Matching placebo". "Overall treatment preference was assessed by the patient under double-blind conditions" at end of study
Incomplete outcome data (attrition bias) All outcomes	High risk	Imputation method not reported. Completer analysis for efficacy data
Size	High risk	50 participants in each treatment arm, but only 38 provided data for analysis

Watson 2003

Methods	Two-centre, randomised, double-blind, active placebo-controlled, cross-over study

Watson 2003 *(Continued)*

	Study duration: washout 2 to 7 days then treatment phase of 2 periods of 4 weeks, without washout at cross-over
Participants	Diabetic with symmetrical, distal sensory neuropathy At least moderate PI (≥ 2/5) at screening for ≥ 3 months Stable glycaemic control Exclusions: pain of other aetiology, opioid allergy or intolerance, history of drug or alcohol abuse N = 45 Mean (± SD) age: 63 (± 9) years M 19, F 17 Mean (± SD) baseline pain 67/100 (± 15)
Interventions	All pre-study opioid drugs discontinued 2 to 7 days before randomisation Other stable medications continued Oxycodone MR to maximum 80 mg/day, n = 45 Placebo (benztropine) to maximum 2 mg/day, n = 45 Starting dose oxycodone 10 mg, twice daily or benztropine 0.25 mg. Upward titration by 10 mg (oxycodone) or 0.25 mg (benztropine) twice daily every 2 to 7 days Rescue medication - paracetamol Mean (± SD) daily dose in last week of study: Oxycodone 40 (± 19) mg Benztropine 1.2 (± 0.6) mg, (49 (± 24) mg placebo)
Outcomes	Successful treatment defined as at least moderate pain relief (the top 3 categories) on a 6-point categorical scale (worse pain, no relief, slight, moderate, a lot, complete) Diary: • Daily overall PI (100 mm VAS and 5-point categorical scale) • Daily overall pain relief (6-point categorical scale) • Intensity of steady, brief, and skin pain over previous week (100 mm VAS and 5-point categorical scale) • Rescue medication used Weekly: Disability (Pain Disability Index) At baseline, cross-over, and end of study: SF-36 Pain and sleep questionnaire Adverse events reported spontaneously by participants or observed by investigator At the end of each phase, participants and investigators: Effectiveness (7-point categorical scale) Satisfaction with pain relief and tolerability (yes, no)

Watson 2003 *(Continued)*

	Preference
	Blinding
Notes	Oxford Quality Score: R2, DB1, W1 Total = 4/5
	Recruitment: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	"Study medication prepackaged with assigned randomization numbers", allocated using "consecutive numbers after screening to ensure balanced treatment at both centres"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind" but methods to achieve blinding of medication not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" but methods to achieve blinding of medication not reported. "Test of blinding" by participants and investigators at end of study, details not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Imputation method not reported. Completer analysis for efficacy data
Size	High risk	< 50 participants per treatment arm

BDI: Beck Depression Inventory; BPI: Brief Pain Inventory; DB: double blind; F: female; HbA1c: glycosylated haemoglobin; ITT: intention-to-treat; LOCF: last observation carried forward; M: male; MR: modified-release; N: number of participants in study; n: number of participants in treatment arm; NPS: Neuropathic Pain Scale; PI: pain intensity; POMS: Profile of Mood States; PR: prolonged-release; R: randomisation; SF-36: 36-item Short-Form health survey; VAS: visual analogue scale; W: withdrawals.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Buynak 2010	Not specifically neuropathic pain
EUCTR2004-003752-19-HU	Not specifically neuropathic pain
EUCTR2005-003510-15-DE	No appropriate control, not specifically neuropathic pain
Gatti 2009	Open-label study
Green 2014	Not specifically neuropathic pain
Hale 1999	Not specifically neuropathic pain
Hale 2005	Not specifically neuropathic pain

Study	Reason for exclusion
He 2009	No oxycodone treatment arm. Not specifically neuropathic pain
ISRCTN76170309	Not specifically neuropathic pain
Kopecky 2015	Not specifically neuropathic pain. No response to request (e-mail, 11 January 2016) for further information on study
Lange 2010	Not specifically neuropathic pain
Löwenstein 2009	No appropriate control. Mostly pain of musculoskeletal origin
NCT00414453	Study terminated early. Fewer than 10 participants per treatment arm
NCT00449176	Not specifically neuropathic pain. Pooled results for pain of different origins
NCT00784810	Mostly pain not of neuropathic origin. Pooled results for pain of different origins
NCT01014559	No appropriate control. Pain arising from diverse conditions, including cancer
NCT01427270	No appropriate control. Not neuropathic pain
NCT01427283	No appropriate control. Not neuropathic pain
NCT01438567	No appropriate control. Not specifically neuropathic pain
NCT01439100	Pain in Parkinson's disease, not considered in this review
NCT01502644	Open-label study
NCT02321397	A study of different dosing regimens. Pain arising from diverse conditions, including cancer
Simpson 2008	Pain arising from diverse conditions, fewer than 20% had neuropathic pain, pooled results from pain of different origins
Steiner 2011	Very few participants with neuropathic pain, pooled results from pain of different origins
Vondrackova 2008	Not specifically neuropathic pain, pooled results from pain of different origins
Webster 2006	Not specifically neuropathic pain
Wild 2010	Open-label, and not specifically neuropathic pain
Wörz 2003	Not a randomised controlled trial
Zin 2010	Trial of oxycodone + pregabalin combination therapy (not oxycodone as add-on therapy)

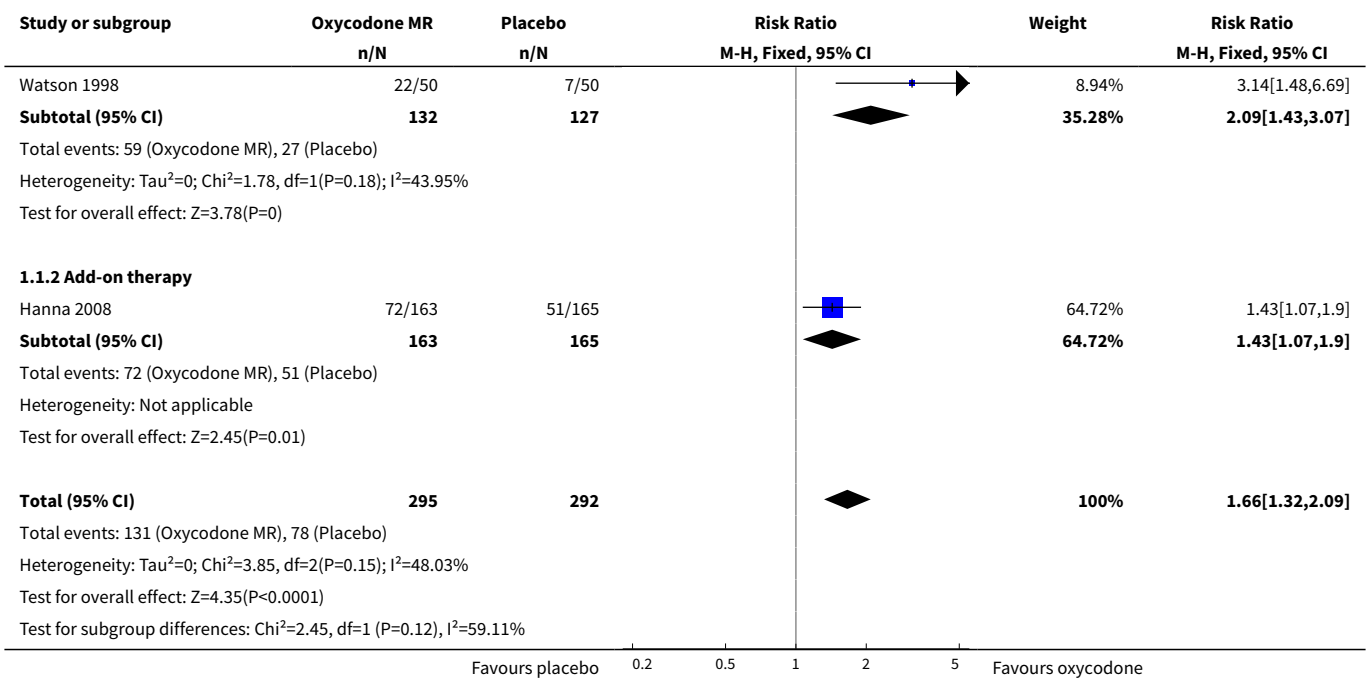
DATA AND ANALYSES

Comparison 1. Oxycodone MR versus placebo

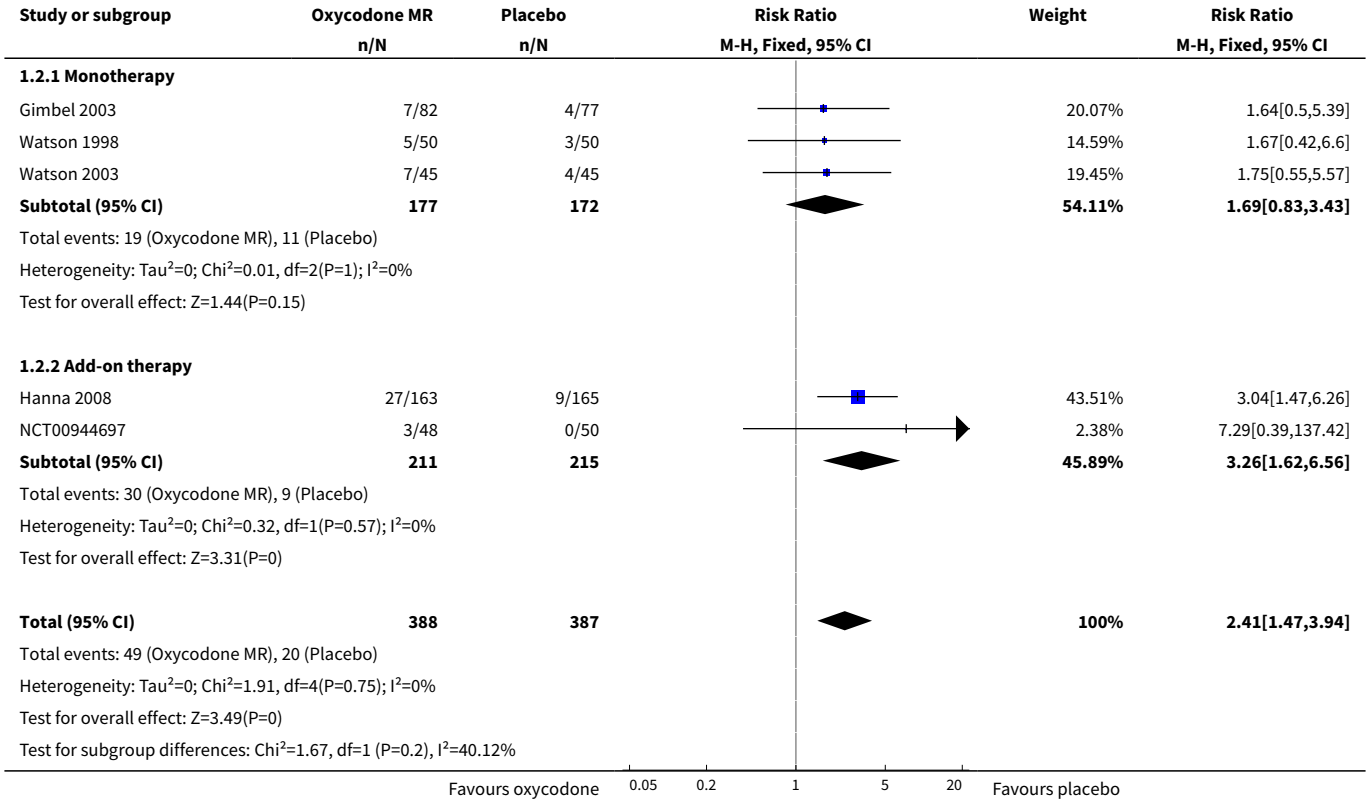
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 At least moderate pain relief	3	587	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [1.32, 2.09]
1.1 Monotherapy	2	259	Risk Ratio (M-H, Fixed, 95% CI)	2.09 [1.43, 3.07]
1.2 Add-on therapy	1	328	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [1.07, 1.90]
2 Adverse event withdrawals	5	775	Risk Ratio (M-H, Fixed, 95% CI)	2.41 [1.47, 3.94]
2.1 Monotherapy	3	349	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.83, 3.43]
2.2 Add-on therapy	2	426	Risk Ratio (M-H, Fixed, 95% CI)	3.26 [1.62, 6.56]
3 Lack of efficacy withdrawals	5	775	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.10, 0.44]
3.1 Monotherapy	3	349	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.03, 0.45]
3.2 Add-on therapy	2	426	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.13, 0.74]
4 Any adverse event	5	782	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [1.24, 1.46]
4.1 Monotherapy	3	349	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.20, 1.54]
4.2 Add-on therapy	2	433	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [1.19, 1.48]
5 Serious adverse events	4	447	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.37, 1.80]
5.1 Monotherapy	3	349	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.18, 1.23]
5.2 Add-on therapy	1	98	Risk Ratio (M-H, Fixed, 95% CI)	9.37 [0.52, 169.45]
6 Specific adverse events	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Constipation	3	584	Risk Ratio (M-H, Fixed, 95% CI)	3.62 [2.41, 5.43]
6.2 Nausea	3	584	Risk Ratio (M-H, Fixed, 95% CI)	2.73 [1.88, 3.95]
6.3 Somnolence	3	584	Risk Ratio (M-H, Fixed, 95% CI)	3.70 [2.33, 5.86]
6.4 Dizziness	3	584	Risk Ratio (M-H, Fixed, 95% CI)	3.31 [1.98, 5.51]

Analysis 1.1. Comparison 1 Oxycodone MR versus placebo, Outcome 1 At least moderate pain relief.

Study or subgroup	Oxycodone MR n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Monotherapy					
Gimbel 2003	37/82	20/77		26.34%	1.74[1.11,2.71]

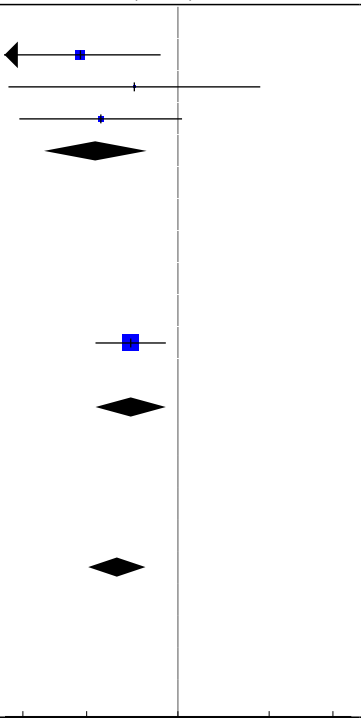


Analysis 1.2. Comparison 1 Oxycodone MR versus placebo, Outcome 2 Adverse event withdrawals.



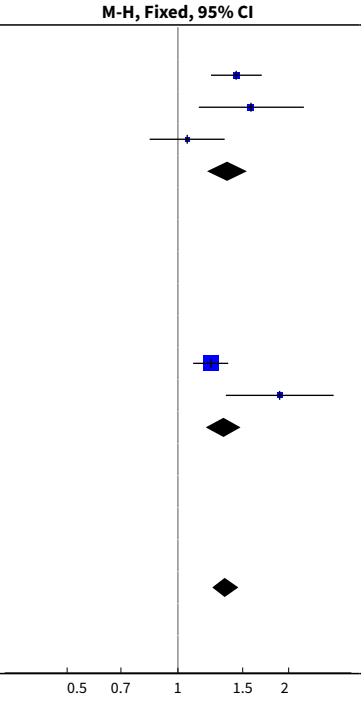
Analysis 1.3. Comparison 1 Oxycodone MR versus placebo, Outcome 3 Lack of efficacy withdrawals.

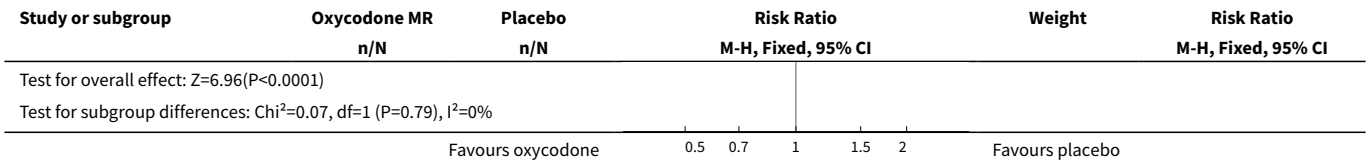
Study or subgroup	Oxycodone MR n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Monotherapy					
Gimbel 2003	1/82	11/77		28.56%	0.09[0.01,0.65]
Watson 1998	0/50	1/50		3.78%	0.33[0.01,7.99]
Watson 2003	1/45	7/45		17.62%	0.14[0.02,1.11]
Subtotal (95% CI)	**177**	**172**		**49.96%**	**0.12[0.03,0.45]**
Total events: 2 (Oxycodone MR), 19 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.52, df=2(P=0.77); I^2=0%					
Test for overall effect: Z=3.16(P=0)					
1.3.2 Add-on therapy					
Hanna 2008	6/163	20/165		50.04%	0.3[0.13,0.74]
NCT00944697	0/48	0/50			Not estimable
Subtotal (95% CI)	**211**	**215**		**50.04%**	**0.3[0.13,0.74]**
Total events: 6 (Oxycodone MR), 20 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.64(P=0.01)					
Total (95% CI)	**388**	**387**		**100%**	**0.21[0.1,0.44]**
Total events: 8 (Oxycodone MR), 39 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.61, df=3(P=0.66); I^2=0%					
Test for overall effect: Z=4.18(P<0.0001)					
Test for subgroup differences: Chi^2=1.24, df=1 (P=0.26), I^2=19.58%					



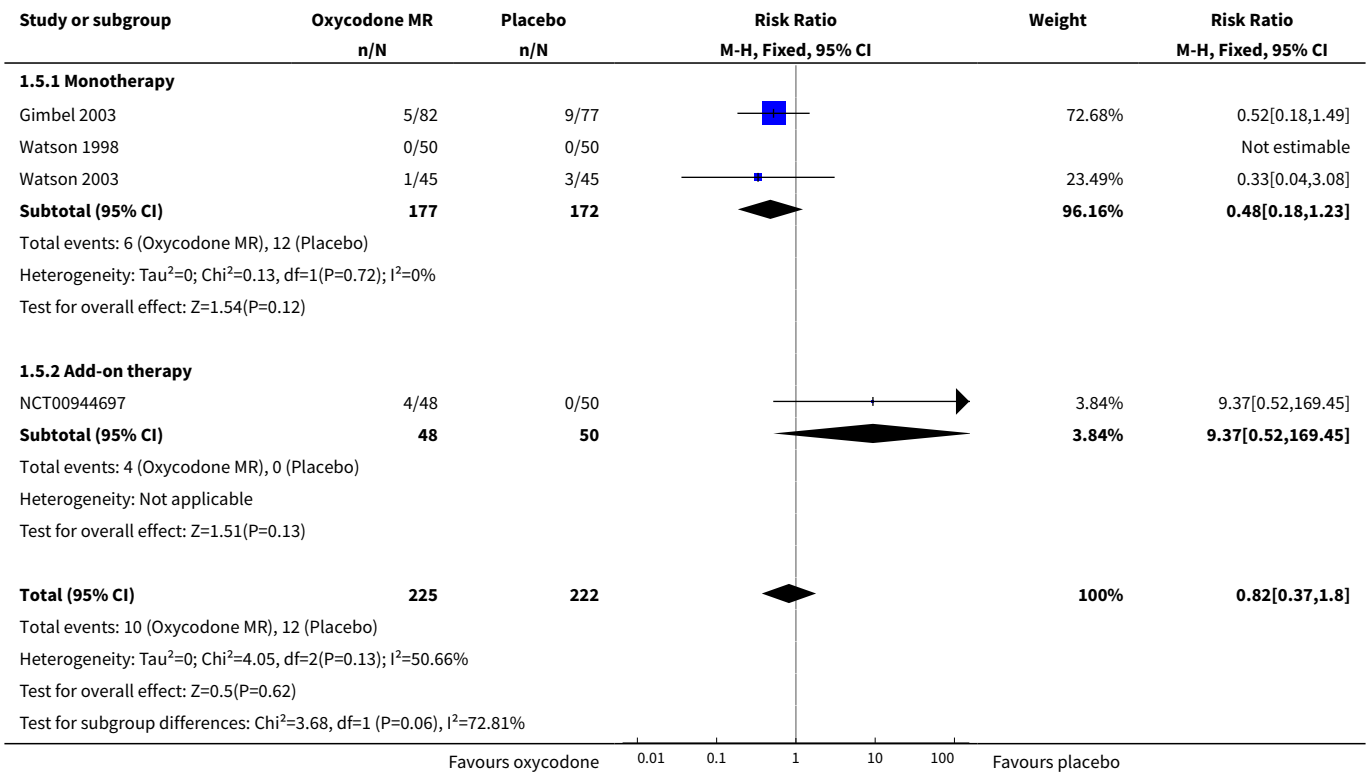
Analysis 1.4. Comparison 1 Oxycodone MR versus placebo, Outcome 4 Any adverse event.

Study or subgroup	Oxycodone MR n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Monotherapy					
Gimbel 2003	80/82	52/77		21.32%	1.44[1.23,1.69]
Watson 1998	38/50	24/50		9.54%	1.58[1.14,2.2]
Watson 2003	35/45	33/45		13.12%	1.06[0.84,1.34]
Subtotal (95% CI)	**177**	**172**		**43.98%**	**1.36[1.2,1.54]**
Total events: 153 (Oxycodone MR), 109 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.67, df=2(P=0.06); I^2=64.71%					
Test for overall effect: Z=4.76(P<0.0001)					
1.4.2 Add-on therapy					
Hanna 2008	147/168	119/167		47.45%	1.23[1.1,1.37]
NCT00944697	40/48	22/50		8.57%	1.89[1.35,2.65]
Subtotal (95% CI)	**216**	**217**		**56.02%**	**1.33[1.19,1.48]**
Total events: 187 (Oxycodone MR), 141 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=6.17, df=1(P=0.01); I^2=83.78%					
Test for overall effect: Z=5.08(P<0.0001)					
Total (95% CI)	**393**	**389**		**100%**	**1.34[1.24,1.46]**
Total events: 340 (Oxycodone MR), 250 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=12.09, df=4(P=0.02); I^2=66.92%					

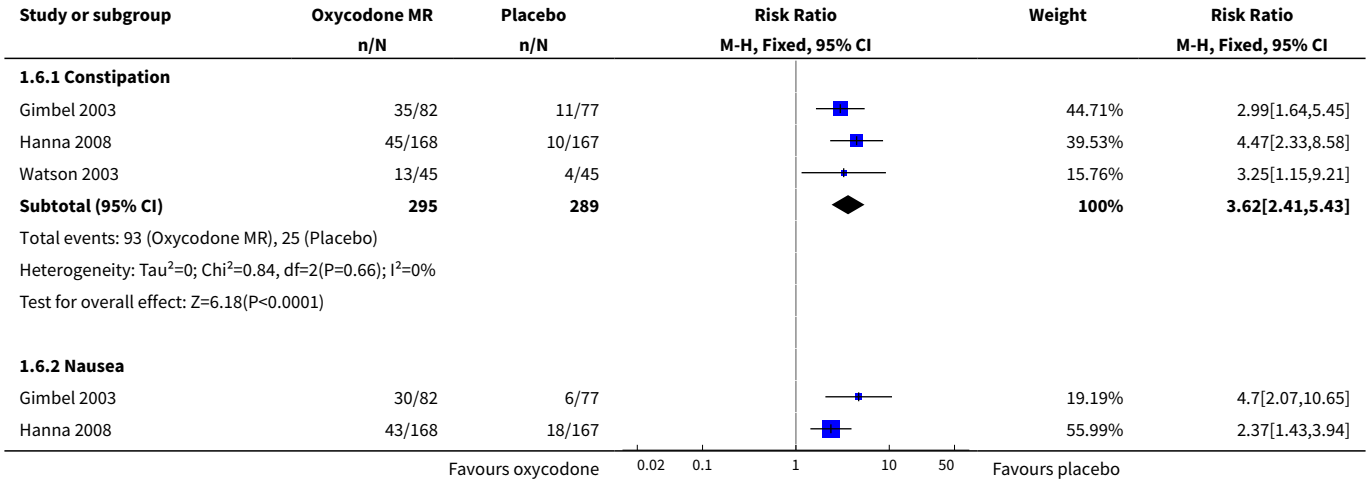


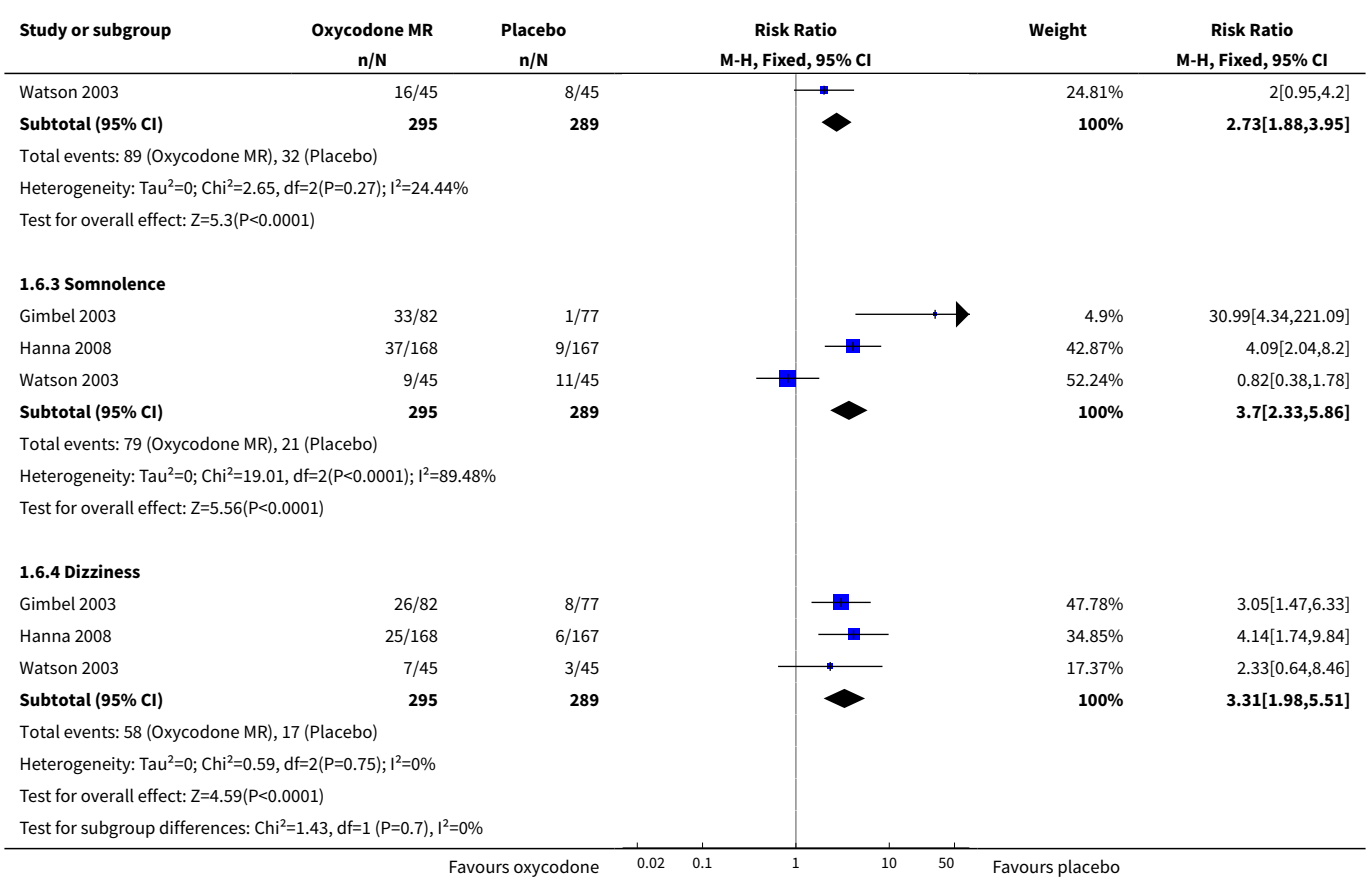


Analysis 1.5. Comparison 1 Oxycodone MR versus placebo, Outcome 5 Serious adverse events.



Analysis 1.6. Comparison 1 Oxycodone MR versus placebo, Outcome 6 Specific adverse events.





APPENDICES

Appendix 1. Methodological considerations for chronic pain

There have been changes in how efficacy of conventional and unconventional treatments is assessed in chronic painful conditions. The outcomes are now better defined, particularly with new criteria of what constitutes moderate or substantial benefit (Dworkin 2008); older trials may only report participants with "any improvement". Newer trials tend to be larger, avoiding problems from the random play of chance. Newer trials also tend to be longer, up to 12 weeks, and longer trials provide a more rigorous and valid assessment of efficacy in chronic conditions. New standards have evolved for assessing efficacy in neuropathic pain, and we are now applying stricter criteria for inclusion of trials and assessment of outcomes, and are more aware of problems that may affect our overall assessment. To summarise some of the recent insights that must be considered in this new review.

- Pain results tend to have a U-shaped distribution rather than a bell-shaped distribution. This is true in acute pain (Moore 2011a; Moore 2011b), back pain (Moore 2010b; Moore 2010e), and arthritis (Moore 2010c); in all cases, average results usually describe the experience of almost no-one in the trial. Data expressed as averages are potentially misleading, unless they can be proven to be suitable.
- As a consequence, we have to depend on dichotomous results (the individual either has or does not have the outcome) usually from pain changes or patient global assessments. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group has helped with their definitions of minimal, moderate, and substantial improvement (Dworkin 2008). In arthritis, trials shorter than 12 weeks, and especially those shorter than eight weeks, overestimate the effect of treatment (Moore 2010c); the effect is particularly strong for less effective analgesics, and this may also be relevant in neuropathic-type pain.
- The proportion of people with at least moderate benefit can be small, even with an effective medicine, falling from 60% with an effective medicine in arthritis, to 30% in fibromyalgia (Moore 2009; Moore 2010c; Moore 2013b; Moore 2014d; Straube 2008; Sultan 2008). One Cochrane review of pregabalin in neuropathic pain and fibromyalgia demonstrated different response rates for different types of chronic pain (higher in diabetic neuropathy and postherpetic neuralgia and lower in central pain and fibromyalgia) (Moore 2009). This indicates that different neuropathic pain conditions should be treated separately from one another, and that pooling should not be done unless there are good grounds for doing so.

- Imputation methods such as last observation carried forward (LOCF), used when participants withdraw from clinical trials, can overstate drug efficacy especially when adverse event withdrawals with drug are greater than those with placebo (Moore 2012b).
- Individual patient analyses and other evidence indicate that people who get good pain relief (moderate or better) have major benefits in many other outcomes, affecting quality of life in a significant way (Moore 2010d; Moore 2014a).

Appendix 2. Search strategy for CENTRAL (via CRSO)

1. MESH DESCRIPTOR oxycodone (358)
2. (oxycodone or OxyNorm or OxyContin or Dinarkon or Endone or Endocodone or Oxygesic or OxyFast or Proladone or Percolone or Roxicodone or Supeudol or Tylox):TI,AB,KY (903)
3. 1 OR 2 (903)
4. MESH DESCRIPTOR Pain EXPLODE ALL TREES (30313)
5. MESH DESCRIPTOR Peripheral Nervous System Diseases EXPLODE ALL TREES (2590)
6. MESH DESCRIPTOR Somatosensory Disorders EXPLODE ALL TREES (710)
7. (pain* or neuralgi* or analgesi* or discomfort*):TI,AB,KY (91633)
8. 4 OR 5 OR 6 OR 7 (98114)
9. 3 AND 8 (826)
10. 2013 TO 2016:YR (122042)
11. 9 AND 10 (249)

For additional searches to 2013 for studies combining oxycodone and naloxone, we replaced line 2 with: (oxycodone and naloxone) OR Targin*

Appendix 3. Search strategy for MEDLINE (via Ovid)

1. Oxycodone/ (575)
2. (oxycodone or OxyNorm or OxyContin or Dinarkon or Endone or Endocodone or Oxygesic or OxyFast or Proladone or Percolone or Roxicodone or Supeudol or Tylox).mp. (880)
3. 1 or 2 (880)
4. exp Neuralgia/ (3964)
5. exp PERIPHERAL NERVOUS SYSTEM DISEASES/ (19461)
6. exp SOMATOSENSORY DISORDERS/ (4309)
7. (pain* or neuralgi* or analgesi* or discomfort*).mp. (129081)
8. 4 or 5 or 6 or 7 (141965)
9. randomized controlled trial.pt. (96197)
10. randomized.ab. (86970)
11. randomly.ab. (56988)
12. controlled clinical trial.pt. (7525)
13. 9 or 10 or 11 or 12 (174731)
14. 3 and 8 and 13 (187)
15. limit 14 to yr="2013 -Current" (94)

For additional searches to 2013 for studies combining oxycodone and naloxone, we replaced line 2 with: (oxycodone and naloxone) OR Targin*

Appendix 4. Search strategy for EMBASE (via Ovid)

1. Oxycodone/ (10909)
2. (oxycodone or OxyNorm or OxyContin or Dinarkon or Endone or Endocodone or Oxygesic or OxyFast or Proladone or Percolone or Roxicodone or Supeudol or Tylox).mp. (11593)
3. 1 or 2 (11593)
4. exp neuropathy/ (306727)
5. (pain* or neuralgi* or analgesi* or discomfort*).mp. (882602)
6. 4 or 5 (1106811)
7. crossover-procedure/ (41207)
8. double-blind procedure/ (101424)
9. randomized controlled trial/ (346095)
10. (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or (doubl* adj blind*) or assign* or allocat*).tw. (1181238)

11.7 or 8 or 9 or 10 (1249122)
12.3 and 6 and 11 (1668)
13.limit 14 to yr="2013 -Current" (467)

For additional searches to 2013 for studies combining oxycodone and naloxone, we replaced line 2 with: (oxycodone and naloxone) OR Targin*

Appendix 5. GRADE: criteria for assigning grade of evidence

The GRADE system uses the following criteria for assigning grade of evidence (GRADEpro GDT 2016).

- **High** = further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate** = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low** = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very low** = any estimate of effect is very uncertain.

We decrease grade if we find:

- a serious (-1) or very serious (-2) limitation to study quality;
- important inconsistency (-1);
- some (-1) or major (-2) uncertainty about directness;
- imprecise or sparse data (-1);
- a high probability of reporting bias (-1).

We increase grade if we find:

- strong evidence of association - significant risk ratio of > 2 (< 0.5) based on consistent evidence from two or more; observational studies, with no plausible confounders (+1);
- very strong evidence of association - significant risk ratio of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2);
- evidence of a dose response gradient (+1);
- that all plausible confounders would have reduced the effect (+1).

In addition, there may be circumstances where the overall rating for a particular outcome needs to be adjusted as recommended by GRADE guidelines (Guyatt 2013a). For example, if there are so few data that the results are highly susceptible to the random play of chance, or if a studies use LOCF imputation in circumstances where there are substantial differences in adverse event withdrawals, one would have no confidence in the result, and would need to downgrade the quality of the evidence by 3 levels, to very low quality. In circumstances where there were no data reported for an outcome, we would report the level of evidence as very low quality (Guyatt 2013b).

Appendix 6. Summary of efficacy in individual studies

Study	Treatment	Pain outcome	Other efficacy outcome
Gimbel 2003	Oxycodone MR to maximum 120 mg/day, n = 82 Placebo, n = 77 Titration over 42 days	Mean (SE) of average daily pain intensity (days 28 to 42): Oxycodone MR 4.1 (0.3) Placebo 5.3 (0.3) Median time to achieve mild pain: Oxycodone MR 6 days Placebo 17 days Mean (SD) days with mild pain: Oxycodone MR 20 (17) days Placebo 13 (16) days	Oxycodone MR significantly better than placebo for all other outcomes except physical functioning, general health, and mental health of SF-36, and on subscales of Rand Mental Health Inventory

(Continued)

		Mean percentage (SD) days with mild pain: Oxycodone MR 47 (39) % Placebo 29 (37) % Additional data (Jensen 2006, see Gimbel 2003); responder analysis ≥ 33% reduction in pain intensity at 6 weeks: Oxycodone MR responder 37/82, non-responder 45/82 Placebo responder 20/77, non-responder 57/77	
Hanna 2008	Current dose of gabapentin continued (similar across groups, < 1200 mg/day to > 1800 mg/day) Oxycodone PR, n = 163 Placebo, n = 165 (full analysis population)	Mean reduction in pain score (0 to 10 scale) at 12 weeks Oxycodone PR 2.1 Placebo 1.5 "Equivalent to a 33% reduction in pain"	Global assessment of pain (good or very good) Oxycodone PR 72/121 Placebo 51/127 ITT: Oxycodone PR 72/163 Placebo 51/165 "Participants who did not complete rated less favourably"
NCT00944697	Oxycodone/naloxone MR, n = 48 Placebo, n = 50 Dose/titration not specified	Short Form McGill Pain Score (0 to 150; high worse pain) at 12 weeks Oxycodone MR 48/150 (SD 30) Placebo 50/150 (SD 30)	None provided
Watson 1998	Oxycodone MR to maximum 60 mg/day, n = 50 Placebo, n = 50 Titration in each of 2 periods of 4 weeks, without washout at cross-over	For participants with data from both phases only Mean daily overall pain intensity in last week of study: Oxycodone MR 35 (± 25)/100 Placebo 54 (± 25)/100 Participants with at least moderate pain relief (at least 3 on a scale of 0 to 5) ITT: Oxycodone MR 22/50 (58% of completers) Placebo 7/50 (18% of completers)	Oxycodone MR better than placebo for disability No difference in mood factors of POMS or in BDI Preference: Oxycodone MR 67% Placebo 11% No preference 22%
Watson 2003	Oxycodone MR to maximum 80 mg/day, n = 45 Placebo (benztropine) to maximum 2 mg/day, n=45	Mean (SD) pain intensity in last week of phase: Oxycodone MR: 21.8 (20.7) Placebo: 48.6 (26.6) "Successful treatment" defined as at least moderate pain relief using 6 point scale, NNT 2.6 (no CI) reported, almost certainly based on "evaluable"	All other results reported as group means. Oxycodone MR better than placebo, for all but a few domains of sleep, disability, and SF-36 Oxycodone MR preferred by 88%, rated moderately or highly effective by 95%, and

(Continued)

	Titration in each of 2 periods of 4 weeks, without washout at cross-over	population (n = 36) who completed ≥ 1 week of 2nd phase	73% were satisfied. No data for placebo 88% of participants and investigators correctly guessed treatment assignment

BDI: Beck Depression Inventory; BPI: Brief Pain Inventory; CI: confidence interval; ITT: intention-to-treat; MR: modified release; n: number of participants per treatment arm; NNT: number needed to treat for an additional beneficial outcome; POMS: Profile of Mood States; PR: prolonged release; SD: standard deviation; SE: standard error; SF-36: 36-item short-form health survey.

Appendix 7. Summary of adverse events and withdrawals in individual studies

Study	Treatment	Adverse events	Withdrawals
Gimbel 2003	Oxycodone MR to maximum 120 mg/day, n = 82 Placebo, n = 77 Titration over 42 days	Any AE: Oxycodone MR: 80/82 Placebo: 52/77 SAE: Oxycodone MR: 5/82 (including 1 death) Placebo: 9/77 No SAE judged related to study medications Deaths: Oxycodone MR 1/82 Specific AE occurring in ≥ 10% participants Constipation: oxycodone MR 35/82; placebo 11/77 Somnolence: oxycodone MR 33/82; placebo 1/77 Nausea: oxycodone MR 30/82; placebo 6/77 Dizziness: oxycodone MR 26/82; placebo 8/77 Pruritus: oxycodone MR 20/82; placebo 6/77 Vomiting: oxycodone MR 17/82; placebo 2/77 Dry mouth: oxycodone MR 13/82; placebo 2/77 Asthenia: oxycodone MR 12/82; placebo 5/77 Headache: oxycodone MR 9/82; placebo 18/77	AE: Oxycodone MR: 7/82 Placebo: 4/77 LoE: Oxycodone MR: 1/82 Placebo: 11/77 Other: Oxycodone MR: 11/82 Placebo: 10/77
Hanna 2008	Current dose of gabapentin continued (similar across groups, < 1200 mg/day to > 1800 mg/day)	Any AE: Oxycodone PR 147/168 Placebo 119/167 Some SAEs occurred, but none considered related to study drug In ≥ 10% participants	All cause: Oxycodone PR 42/163 Placebo 37/165 AE: Oxycodone PR 27/163

(Continued)

	Oxycodone PR, n = 163 Placebo, n = 165 (full analysis population)	Constipation: oxycodone PR 45/168; placebo 10/167 Nausea: oxycodone PR 43/168; placebo 18/167 Vomiting: oxycodone PR 16/168; placebo 7/167 Fatigue: oxycodone PR 31/168; placebo 14/167 Dizziness: oxycodone PR 25/168; placebo 6/167 Somnolence: oxycodone PR 37/168; placebo 9/167 Headache: oxycodone PR 17/168; placebo 17/167	Placebo 9/165 LoE: Oxycodone PR 6/163 Placebo 20/165 Administrative/participant choice: Oxycodone PR 9/163 Placebo 8/165
NCT00944697	Oxycodone/naloxone MR, n = 48 Placebo, n = 50 Dose/titration not specified	Any AE (excluding SAE): Oxycodone MR 36/48 Placebo 22/50 SAE: Oxycodone MR 4/48 Placebo 0/50 Deaths: none Gastrointestinal: Oxycodone MR 17/48 Placebo 10/50 Nervous system disorders: Oxycodone MR 12/48 Placebo 5/50	All cause: Oxycodone MR 5/48 Placebo 2/50 AE: Oxycodone MR 3/48 Placebo 0/50 LoE: none reported Administrative/participant choice: Oxycodone MR 2/48 Placebo 2/50
Watson 1998	Oxycodone MR to maximum 60 mg/day, n = 50 Placebo, n = 50 Titration in each of 2 periods of 4 weeks, without washout at crossover	Any AE: Oxycodone MR: 38/50 Placebo: 24/50 SAE: none reported Deaths: none reported Most frequent AE with oxycodone: constipation (5/50), nausea (4/50), sedation (3/50) No data reported for placebo	AE: Oxycodone: MR 5/50 Placebo: 3/50 LoE: Oxycodone MR: 0/50 Placebo: 1/50 Other: Oxycodone MR: 1/50 Placebo: 1/50
Watson 2003	Oxycodone MR to maximum 80 mg/day, n = 45 Placebo (benztropine) to max-	Any AE: Oxycodone MR: 35/45 Placebo: 33/45 SAE:	AE: Oxycodone MR: 7/45 Placebo: 4/45 LoE:

(Continued)

	imum 2 mg/day, n=45 Titration in each of 2 periods of 4 weeks, without washout at cross-over	Oxycodone MR: 1/45 Placebo: 3/45 Specific AE occurring in ≥ 5 participants: Nausea: oxycodone MR 16/45; placebo 8/45 Somnolence: oxycodone MR 9/45; placebo 11/45 Constipation: oxycodone MR 13/45; placebo 4/45 Dry mouth: oxycodone MR 3/45; placebo 12/45 Diarrhoea: oxycodone MR 4/45; placebo 6/45 Dizziness: oxycodone MR 7/45; placebo 3/45 Headache: oxycodone MR 5/45; placebo 3/45 Asthenia: oxycodone MR 2/45; placebo 5/45 Vomiting: oxycodone MR 5/45; placebo 2/45 Insomnia: oxycodone MR 3/45; placebo 4/45 Pruritus: oxycodone MR 4/45; placebo 1/45 Sweating: oxycodone MR 4/45; placebo 1/45	Oxycodone MR: 1/45 Placebo: 7/45 Other: Oxycodone MR: 2/45 Placebo: 0/45

AE: adverse event; MR: modified release; LoE: lack of efficacy; SAE: serious adverse event.

WHAT'S NEW

Date	Event	Description
25 July 2016	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 8, 2013
Review first published: Issue 6, 2014

Date	Event	Description
3 March 2016	New citation required and conclusions have changed	New studies added, providing data for efficacy analysis and additional data for adverse events and withdrawals analyses.
21 December 2015	New search has been performed	Original review split into separate reviews of neuropathic pain and fibromyalgia pain. This review considers neuropathic pain only. Inclusion criteria expanded to include studies using oxycodone in fixed dose combination with naloxone and as add-on therapy to stable, inadequate treatment with an another class of drug. New searches identified new studies.

Date	Event	Description
3 July 2014	Amended	Source of support added

CONTRIBUTIONS OF AUTHORS

SD and RAM wrote the protocol.

For the original review, HG and SD searched for and selected studies for inclusion and carried out data extraction. All review authors were involved in the analysis and in writing the full review.

For this update, HG and SD searched for and selected studies for inclusion and carried out data extraction. HG, SD, and RAM carried out analysis. All review authors were involved in writing the full review.

This review will now be made stable, with no further updates planned.

DECLARATIONS OF INTEREST

HG: none known.

SD: none known.

CS none known; CS is a specialist pain physician and manages patients with neuropathic pain.

RAM has received grant support from RB relating to individual patient level analyses of trial data on ibuprofen in acute pain and the effects of food on drug absorption of analgesics (2013), and from Grünenthal relating to individual patient level analyses of trial data regarding tapentadol in osteoarthritis and back pain (2015). He has received honoraria for attending boards with Menarini concerning methods of analgesic trial design (2014), with Novartis (2014) about the design of network meta-analyses, and RB on understanding pharmacokinetics of drug uptake (2015).

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Relief Trust, UK.

  General institutional support

External sources

- The National Institute for Health Research (NIHR), UK, UK.

  NIHR Cochrane Programme Grant: 13/89/29 - Addressing the unmet need of chronic pain: providing the evidence for treatments of pain.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the original review:

We changed the list of examples of neuropathic pain conditions to stress that the inclusion criteria were broad; however, we identified few studies, and were able to include data from only two conditions in the review.

We intended to use two tiers to assess evidence, depending on quality criteria. We have now split the lower tier in two, making three separate tiers. Entry criteria for the first tier were high and we were concerned that evidence of widely varying quality would (necessarily) all be grouped together in the lower of a two tier hierarchy. To make best use of such second tier evidence, it seems appropriate to use three rather than two tiers. The revised criteria are described in the Methods section. Unfortunately, only third tier evidence was available for this review.

For the 2016 update:

The protocol included both neuropathic pain and fibromyalgia, but has been split at update. This review considers only neuropathic pain conditions. We have removed CRPS Type I from the list of neuropathic pain conditions because it is no longer considered to satisfy criteria for neuropathic pain. There was no effect of the content of the review since we did not find any relevant studies in CRPS Type I.

In the earlier review, we did not include oxycodone in fixed dose combination with naloxone (to reduce constipation). However, there are now a number of studies indicating that the addition of naloxone does not affect analgesic efficacy in a variety of painful conditions, so we included it in our updated searches. We planned to analyse data separately for oxycodone and the combination, but only one study using this combination satisfied our inclusion criteria.

We have also included studies using oxycodone (alone or in combination with naloxone) as an add-on therapy to stable, but inadequate (at least moderate pain intensity) treatment with a different class of drug (such as an antiepileptic or antidepressant drug). Two studies using this design satisfied our inclusion criteria, and we analysed these as a subgroup.

We have included additional information about the methods used to assess the quality of the evidence using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system.

No sensitivity analyses were planned for this review, but because we combined data from the study in postherpetic neuralgia with those in diabetic neuropathy for this update, we carried out sensitivity analyses (where there were sufficient data) to determine the effect of excluding postherpetic neuralgia. In addition, because one study used an 'active' placebo, we carried out sensitivity analyses (where there were sufficient data) to determine whether this had any effect on the incidence of adverse events.

NOTES

A new search within two years is not likely to identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. If appropriate, we will update the review again if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics, Opioid [adverse effects] [*therapeutic use]; Constipation [chemically induced] [epidemiology]; Delayed-Action Preparations [therapeutic use]; Diabetic Neuropathies [*drug therapy]; Disorders of Excessive Somnolence [chemically induced] [epidemiology]; Dizziness [chemically induced] [epidemiology]; Nausea [chemically induced] [epidemiology]; Neuralgia, Postherpetic [drug therapy]; Oxycodone [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Aged; Female; Humans; Male; Middle Aged